Why stress causes psychosis and psychosis causes stress

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Voor Koen, Eline en het kleine wondertje in mijn buik

Paranimfen
Dagmar Versmissen
Sera Langenveld

CONTENTS

Chapter 1

Introduction

Phenomenology of psychosis

The term psychosis refers to a condition in which a person is losing contact with reality. Two of the most distinctive symptoms of psychosis are delusions and hallucinations. A delusion is a fixed false belief, such as the incorrect paranoid belief that someone is trying to harm you. Hallucinations are sensory experiences without an external stimulus being present, for example hearing voices. Several different psychotic disorders can be distinguished, the most important being schizophrenia, schizoaffective disorder and schizophreniform disorder. Psychotic disorders are some of the most severe mental illnesses, mostly affecting young people. Psychotic disorders affect approximately three percent of the population (Perala et al. 2007).
In clinical practice, psychosis is viewed as a dichotomous concept: you either have a psychotic disorder or you do not. This view is obviously driven by the medical decision a doctor has to make: does this person need treatment, yes or no? However, it has been suggested that psychosis may exist as a continuum in nature (Johns and van Os 2001; Allardyce et al. 2007; van Os et al. 2009). Reviewing the literature, a phenotypic continuum appears to exist ranging from no psychotic experiences over psychotic experiences (prevalence of about 8 %) and psychotic symptoms (prevalence around 4%) to a clinical psychotic disorder (prevalence 3%) (van Os et al. 2009). The notion of a psychosis continuum is supported by the fact that similar associations with demographic characteristics, such as age, sex and ethnicity, are found for psychotic symptoms and subclinical psychotic experiences (van Os et al. 2009). A second argument is that the same risk factors are involved in both the development of psychotic disorders as well as psychotic-like experiences and schizotypy (van Os et al. 2003; Janssen et al. 2004; Johns et al. 2004).

Stress and psychosis

For a long time, stress has been implicated in the aetiology of psychosis. According to the vulnerability-stress model (Zubin and Spring 1977; Zubin et al. 1983), psychiatric symptoms will emerge whenever a threshold of stressors exceeds the individual's vulnerability level, the latter being a stable characteristic. Several lines of evidence have supported the notion that stress is involved in the development of psychotic symptoms. In the general population, adverse life events have been associated with the emergence of psychotic symptoms, both cross-sectionally and longitudinally (Johns et al. 2004; Wiles et al. 2006). For patients with a psychotic disorder, increased numbers of major life events have been associated with higher levels of symptomatology and increased relapse rates (Myin-Germeys et al. 2003). Other environmental factors, which could be proxies for social stress, have also been im-

plicated. For example, growing up in an urban environment is a risk factor for the development of a psychotic disorder (Marcelis et al. 1999; Kirkbride et al. 2006). Also, other stressful events such as discrimination, migration, childhood trauma or bullying have been associated with clinical and sub-clinical psychosis (Janssen et al. 2003; Janssen et al. 2004; Read et al. 2005; Lataster et al. 2006; Weiser et al. 2008). This epidemiological research has clearly identified environmental stressors as risk factor for psychosis. However, these studies provide no insight in the exact mechanisms. How do these stressors interact with the vulnerable person, eventually resulting in psychosis? A series of studies by our group investigated how small stressful experiences occurring in daily life impacted on subjects with varying degrees of vulnerability for psychosis. First, one study investigated negative and positive affect after daily life stress, called emotional reactivity to stress, in patients with a psychotic disorder in remission, first-degree relatives of patients and a healthy control group ((Myin-Germeys et al. 2001). The results showed that higher levels of familial risk for psychosis were associated with higher levels of emotional reactivity to daily life stress (Myin-Germeys et al. 2001). In a recent study, these findings were extended to twins scoring high on a schizotypy measure, a group at of people who have an increased psychometric risk for developing a psychotic disorder (Lataster et al. 2009). Another recent study has further shown that stress-reactivity clusters within families of patients with non-affective psychosis (Lataster et al. submitted). Several studies furthermore show that increased stress-reactivity appears to be an unconfounded, and partially independent mechanism of risk specifically underlying the positive symptoms of psychosis (Lataster et al. submitted). Finally, patients and their first-degree relatives not only show increased emotional reactivity after daily life stress, but they also have increased levels of psychotic symptoms after the occurrence of stressful experiences in daily life, a process which can be called behavioural sensitization (Myin-Germeys et al. 2005).

In conclusion, there is growing body of evidence supporting the vulnerability-stress model. Epidemiological research identified several environmental risk factors for psychosis, and most of these risk factors seem to involve stress. In addition, momentary assessment research provided more insight in the effect that small, daily stressors might have on the vulnerable person. However, several questions remain unanswered. A first, and very important question, is whether we could combine the findings from epidemiology and momentary assessment research. How do environmental stressors impact on the momentary stress-sensitivity and would this be important in the development of psychosis? Collip et al (2008) argued that sensitization might be a central underlying pathway leading from environmental stress to psychosis. Senisitization is a process through which *previous* exposure to adversity or stress makes individuals more sensitive or responsive rather than more resistant

to the *later* occurrence of stress (Collip et al. 2008). Although this seems an attractive hypothesis, evidence to date is lacking. Second, the biological mechanisms underlying this increased stress-response remain unclear. Almost no research to date has focused on possible biological pathways, underlying the association between stress and psychosis. Third, a very important, but often discarded cause of stress are the psychotic symptoms themselves. Hearing voices commenting in your head or being afraid that someone would poison you, could cause enormous amounts of distress. It is therefore important to investigate how patients deal with these forms of stress as well.

Childhood trauma as a risk factor

The term 'childhood trauma' refers to negative life experiences in childhood or adolescence, including physical, sexual and emotional abuse, as well as physical and emotional neglect. A recent interdisciplinary review has shown that childhood trauma is associated with several psychological difficulties and/ or physical problems later in life, such as eating disorders, substance abuse, phobias, irritable bowel syndrome, and autoimmune disorders (Mulvihill 2005). Studies investigating patient samples as well as general population samples have shown that there is also an association between traumatic experiences in childhood and the development of clinical and nonclinical psychotic symptoms (Bebbington et al. 2004; Janssen et al. 2004; Spauwen et al. 2006; Kelleher et al. 2008). Other forms of childhood maltreatment, such as being bullied by peers, have also been associated with increased subclinical psychotic symptoms in adolescents of the general population (Lataster et al. 2006).

To date, only one study has failed to find an association between trauma and psychosis (Spataro et al. 2004). Interestingly, this study was a prospective study using official record data to identify victims of abuse. Although this might seem an advantage at first sight, it might actually have seriously hampered the study. The majority of abuse cases is most likely never registered, meaning that several cases are hidden in the control group. In addition, the identified cases most likely received some form of intervention.

Although it has been proposed that psychosis may be caused by childhood trauma (Read et al. 2005), two recent critical reviews stated that there is not enough evidence to draw this conclusion, because most studies until now have not used appropriate research methods (Morgan and Fisher 2007; Bendall et al. 2008). The main limitations of previous studies are the lack of appropriate control groups, the chronic patient samples and the measurement of trauma (Morgan and Fisher 2007; Bendall et al. 2008). Replication studies are needed using patient samples with re-

cent onset psychosis, including proper control samples, assessing childhood trauma with validated instruments. Another way to move forward, would be to unravel the underlying mechanism.

Biological stress mechanism: the HPA-axis

A second step in the study of stress and psychosis is to investigate which biological mechanisms are underlying this association. A central mechanism in the human stress-response is the hypothalamus-pituitary adrenal axis (HPA-axis). It would be interesting to investigate a) whether there are changes in HPA-axis functioning in the subjects who are vulnerable to psychosis, and b) whether possible alterations are related to psychotic symptoms.

The HPA-axis involves three chemical messengers: corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids. In response to stress, cells in the periventricular nucleus of the hypothalamus release CRH, which then stimulates the pituitary to secrete ACTH. In turn, ACTH stimulates the adrenal cortex to release cortisol. Cortisol has several effects throughout the body to bring about the physiological changes in the body that are needed for the fight or flight response (Corcoran et al. 2003). Cortisol has also an effect in the brain, especially in the hippocampus, which is the main part of a negative feedback mechanism dampening HPA-axis activation (Corcoran et al. 2003).

Besides being the result of a stress-response, cortisol is normally secreted in a peak just after awakening and it decreases rapidly thereafter, forming a diurnal cortisol curve. If a person is confronted with a stressor, extra cortisol is secreted, independent of the circadian secretion (Chrousos and Gold 1992).

Several lines of evidence have already suggested an association between HPA-axis functioning alterations and the development of psychosis. For example, illnesses that are associated with elevated cortisol levels (eg Cushing syndrome), but also the administration of corticosteroids, can induce psychotic symptoms (van Winkel et al. 2008; Walker et al. 2008). Changes in cortisol patterns or reactions have also been investigated in patients with psychosis. First, basal cortisol levels appear to be elevated in patients with psychosis (Ryan et al. 2004; Walsh et al. 2005). Second, one study found a difference in daily cortisol patterns between patients and controls (Kaneko et al. 1992), but most studies indicate no such difference (Rao et al. 1995; Jansen et al. 2000). Third, patients seem to have an increased cortisol response to a pharmacological stressor (Walker and Diforio 1997; Elman et al. 1998). However, a blunted response has been reported to a psychological stressor in patients with psychosis (Albus et al. 1982; Breier et al. 1988; Jansen et al. 1998; Jansen et al. 2000; Marcelis et al. 2004) and in a group of patients with schizotypal personality

disorder (Mitropoulou et al. 2004) compared with a control group. Finally, pronounced reductions in the volume of the hippocampus, a brain region that plays an important role in the feedback mechanism of the HPA axis, have been shown (Wright et al. 2000). In sum, findings from previous research suggest dysfunctions of the HPA-axis in psychosis, although the results are still inconclusive.

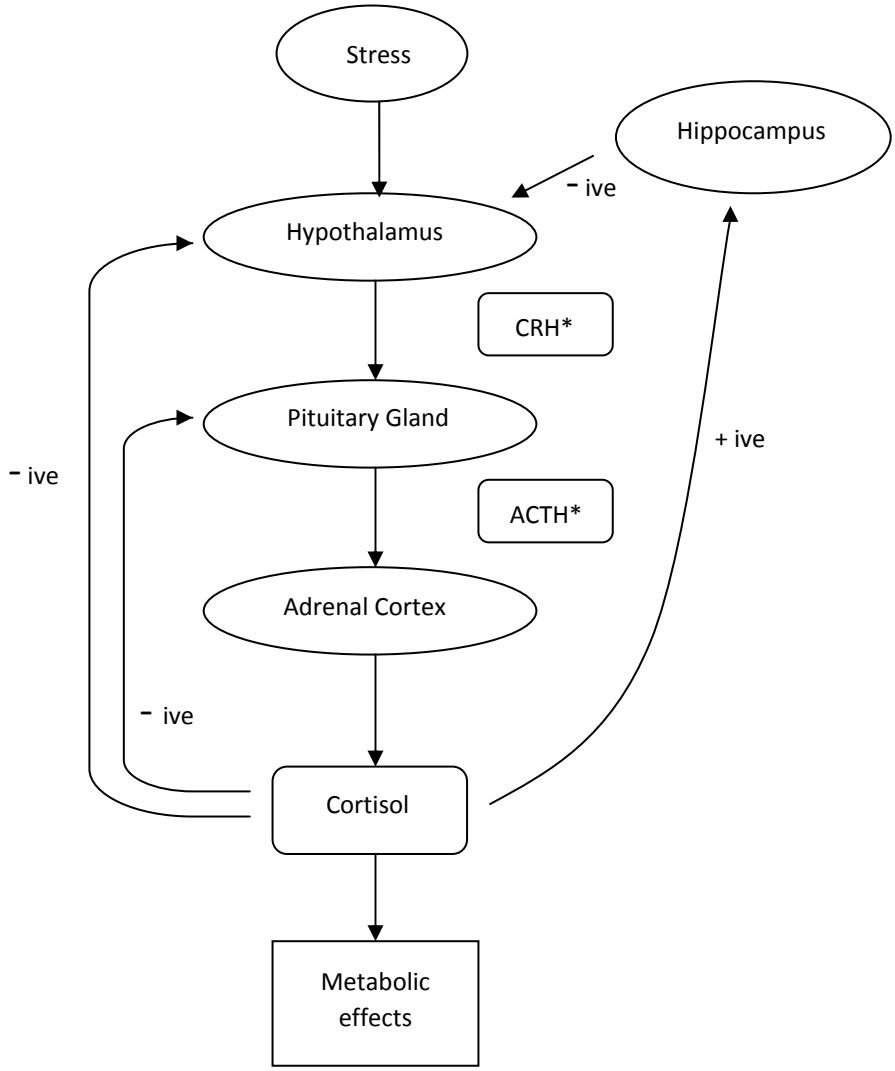

Figure 1. The hypothalamus pituitary adrenal (HPA) axis.

* CRH = corticotropin releasing hormone, ACTH = adrenocorticotropic hormone

A disadvantage of most studies investigating cortisol and HPA-axis functioning in psychosis is that they have studied patients with a psychotic disorder, who almost always take antipsychotic medication. However, the use of antipsychotic medication may influence cortisol levels (Wik 1995). Therefore, studies are needed that study the association between HPA axis activity and psychosis without being confounded by the use of psychotropic medication.

Coping with stress

Finally, stress is not only a risk factor for psychosis, but psychotic symptoms themselves can also be a major cause of distress. Since many patients with a psychotic disorder continue to experience delusions and/or hallucinations regardless of the treatment they receive (Nayani and David 1996), and since patients seem to be more sensitive to stress compared to the general population, it is crucially important to understand how patients cope with these stressful experiences. Coping can be seen as a dynamic process and has previously been described as 'constantly changing cognitive and behavioural efforts to manage specific external and / or internal demands that are appraised as taxing or exceeding the resources of the person' (Lazarus and Folkman 1984). Until now, several studies have investigated the coping mechanisms that psychotic patients use to deal with the distress caused by their symptoms (Falloon and Talbot 1981; Breier and Strauss 1983; Romme and Escher 1989; Romme et al. 1992). For example, Carr (1988) has reported a grouping of five different categories of coping strategies, some of them more successful than others (Carr 1988). One of these categories was symptomatic behaviour, which can be defined as 'any form of behaviour employed with the intention of relieving discomfort but which resulted in the increased expression of illness-related behaviours, such that the outward manifestations of psychopathology would be likely to be augmented rather than concealed or contained' (Carr 1988). More briefly, this latter strategy can be conceived as 'going along with symptoms'; for example people can follow orders from voices or they can keep a knife ready to defend oneself against an imagined persecutor (Carr 1988).

Not all of the identified coping strategies are equally efficient. Especially symptomatic coping appears to be a less effective strategy than other coping strategies. For example, in a group of people from the general population experiencing psychotic symptoms, symptomatic coping was used more often by persons who developed need for care than by persons who did not (Bak et al. 2003). Furthermore, patients with a psychotic disorder who use symptomatic coping experience less control over their symptoms than patients who use non-symptomatic coping strategies (Bak et

al. 2001). Symptomatic coping may therefore be considered to be a relatively non-effective coping method, yet it is has been shown to be the strategy that is by far the most frequent in patients with a psychotic disorder (Bak et al. 2001). Therefore, it is important to investigate whether the use of a symptomatic coping strategies is a stable person characteristic and what the mechanism is that leads to the use of this ineffective strategy.

Investigation of first-degree relatives of patients with psychosis

First-degree relatives of patients with a psychotic disorder have a 10% chance to develop a psychotic disorder themselves, as opposed to a risk of 1% in the general population (Gottesman 1991). This suggests that there is a genetic contribution to the development of psychotic disorders. Furthermore, first-degree relatives also show more schizotypal traits than healthy control subjects (Kendler et al. 1995). As stated previously, these schizotypal or sub-clinical experiences seem to be on a symptomatic but also etiological continuity with more severe psychotic symptoms and disorder. Therefore, they are well suited to study possible underlying mechanisms.

First-degree relatives of patients with psychosis also share several underlying vulnerabilities with their ill relatives, such as neurocognitive deficits (Faraone et al. 1999; Chen and Faraone 2000) and deficits in social cognition (Versmissen et al. 2007; Versmissen et al. 2008). A very important finding for the current thesis is that first-degree relatives, like their ill relatives, tend to react with larger increases in negative emotions and subtle psychotic experiences when they encounter stress in comparison with a healthy control group (Myin-Germeys et al. 2005). Therefore, this group seems well suited to investigate specific mechanisms underlying the association between stress and psychosis. This may be particularly relevant for the study of underlying biological mechanism (the HPA axis), because relatives do not take antipsychotic medication, which may influence the end-product of the HPA axis, cortisol (Meltzer 1989; Wik 1995). Finally, another clear advantage of investigating people at risk is that it allows to examine aetiological factors without the confounds associated with the consequences of the illness (Gooding et al. 2005).

The Experience Sampling Method

Psychosis, stress and coping are all three very complex phenomena, because they all occur in daily life and interact with daily life experiences. Therefore, a very useful method to investigate these concepts is the Experience Sampling Method (ESM)

(Csikszentmihalyi and Larson 1987; Delespaul 1995; Myin-Germeys et al. 2001). ESM is a structured diary method investigating people in the realm of their daily life, using random time-sampling self-assessments. Subjects receive a digital wristwatch and ESM assessment forms collated in a booklet for several days. During the research period, the watch emits a signal (beep) at ten unpredictable moments during the day. After each 'beep', subjects have to stop their activity and fill out the ESM self-assessment forms, collecting reports of thoughts, moods, current context (activity, people present, and location), and severity of symptoms. Using this method, the researcher gets a very detailed view of the daily life of his or her participants.

The ESM is a very useful tool to investigate stress in daily life. First of all, it is possible to study subjective appraisals of stressful events, but also the emotional and psychotic reactions to these stressors can be monitored (van Os et al. 2009). An advantage of the ESM is that, unlike retrospective methods, it is not vulnerable to several biases, such as the recall bias and 'effort-after-meaning'. The recall bias is based on the principle that forgetting is not random and that for example more salient events would be more easily recalled than less salient ones, or that current mood would make mood congruent memories more accessible (Stone and Shiffman 1992; Tourangeau 2000). This bias might be important in psychosis, since it has been consistently shown that patients with psychotic disorder have decreased cognitive capacities, which may even increase their proneness to bias (Krabbendam et al. 2005; Reichenberg and Harvey 2007). 'Effort-after meaning' states that the fact that you already know how situations have evolved might influence your memory of the situation (Stone et al. 1998). By using a method that investigates events at the moments that they occur, these biases cannot occur. Another important advantage of the ESM is that patients are not asked to describe their emotions after a stressful event, but that they answer questions about both experiences simultaneously (together with numerous other questions) and the researcher can analyse possible associations afterwards using the appropriate statistical methods.

Second, since stress reactivity is associated with HPA axis activity and the hormone cortisol (O'Connor et al. 2000), it can also be useful to investigate cortisol using the ESM. Since cortisol can be validly extracted from saliva (Kirschbaum and Hellhammer 1993), subjects can be instructed to take a saliva sample with each beep. The ESM, generating approximately 10 cortisol measures a day, can be an ideal method to investigate the dynamics of the daily cortisol pattern, but also cortisol reactions to stressors can be measured. Also, psychotic symptomatology after changes in cortisol can be investigated (Myin-Germeys et al. 2009).

Finally, until now, coping with the stress generated by psychotic symptoms has mostly been studied retrospectively. However, these retrospective methods are not suitable to assess the dynamic aspects of psychotic symptoms and their related coping process. Since coping with psychotic symptoms is related to how people deal

with the problems in daily life, this can be studied using the ESM (Myin-Germeys et al. 2009).
Despite these advantages of using the ESM, also several questions can be raised about using the Experience Sampling Method. First of all, it can be questioned whether patients suffering from a psychotic disorder are able to use the ESM method. However, previous applications of ESM in schizophrenia (Myin-Germeys et al. 2001; Delespaul et al. 2002; Myin-Germeys et al. 2002) have demonstrated the feasibility, validity and reliability of using the method in this population.
Second, some researchers have questioned the reliability of the paper and pencil ESM method and they have suggested that it would be better to use electronic devices in the sampling process. However, Green et al. have recently demonstrated in a comparative study that both electronic and paper diary methods yield similar results (Green et al. 2006). Also, a very elegant study by Jacobs et al. (Jacobs et al. 2005), using an intensive, random time sampling protocol for salivary cortisol, used electronic monitoring devices to check actual sample times. The results show that 81% of all sampling times were accurately recorded. Furthermore, the same study has also investigated the effects of non-compliance on cortisol results and the results show that inclusion of non-compliant samples in the analysis did not distort the cortisol diurnal profile.

Outline and aims of the thesis

The overall aim of this thesis was to investigate stress in relation to psychosis. First of all, stress involved in the development of psychotic symptoms and the possible mechanism behind this will be the focus of investigation. Secondly, stress caused by the psychotic symptoms and the way people cope with this stress will be investigated.

In *Chapter 2* the putative association between trauma and psychosis and its underlying mechanism will be investigated. The goal of the study described in this chapter was twofold. The first goal was to replicate previous findings of an association between trauma and psychosis. This was done by comparing experiences of trauma in patients with psychosis with a recent onset (<10 years of illness), their first-degree relatives, and healthy control subjects, using a validated instrument, the childhood trauma questionnaire, to assess childhood trauma. The second goal was to investigate sensitization in this sample as a possible mechanism explaining the association between trauma and psychosis.

In *Chapter 3* HPA-axis activity will be investigated as a possible mechanism underlying the association between psychological stress and psychosis. Different aspects of cortisol in the context of normal daily life reality will be investigated in first-degree relatives of patients with psychosis (a group genetically at risk to develop a psychosis) and healthy control subjects. First, basal cortisol level and the cortisol curve over the day will be compared in first-degree relatives and healthy controls. Second, cortisol response to naturally occurring stress will be compared in both groups. Finally, it will be investigated whether elevations in cortisol are related to increased experiences of sub-clinical psychosis.

In *Chapter 4* coping with stress caused by psychotic symptoms will be investigated. Previous studies have shown that most patients use symptomatic coping (i.e. going along with their symptoms). However, this appears to be a less effective strategy than non-symptomatic coping. Therefore, coping with stress in daily life was investigated in 35 patients. This was compared with coping strategies assessed retrospectively that were used to cope with psychotic symptoms.

In *Chapter 5*, a brief summary of the findings is presented. Further, discussion of possible theoretical backgrounds is given. Finally, the implications of the findings and directions for future research are presented.

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Chapter 2

Childhood trauma and increased stress-sensitivity in psychosis: an experience sampling study

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Abstract

Background: The notion that traumatic experiences in childhood (CT) may predict later psychotic outcomes would be strengthened if a plausible mechanism could be demonstrated. Given the fact that previous work has suggested that increased daily life stress-sensitivity is part of the behavioural expression of psychosis liability, the possible mediating role of childhood trauma was investigated. Therefore, this study investigated whether CT, assessed with the Childhood Trauma Questionnaire, increases the risk for psychosis by sensitizing people to daily life stress.
Methods: Fifty psychosis patients, 55 siblings and 45 healthy controls were studied with the Experience Sampling Method in order to assess stress-reactivity in daily life.
Results: Higher levels of CT were found in the patient group. In this group, a significant interaction was found between stress and CT on both negative affect and psychotic intensity, indicating an effect of CT on stress-sensitivity.
Conclusions: Higher rates of trauma in patients versus controls, as well as evidence for an underlying sensitization process, provided further support for the putative association between CT and psychosis.

Introduction

With one recent exception (Spataro et al. 2004), previous epidemiological research has demonstrated an association between childhood trauma and the development of clinical and subclinical psychosis in adulthood and adolescence (Bebbington et al. 2004; Janssen et al. 2004; Lataster et al. 2006; Spauwen et al. 2006; Kelleher et al. 2008). A review article by Read et al. (2005) suggested that the association between trauma and psychosis may be causal, with a dose-effect (Read et al. 2005). However, two recent systematic reviews concluded that methodological flaws in the available studies limit the conclusions that can be drawn with regard to this putative association (Morgan and Fisher 2007; Bendall et al. 2008). One way to strengthen the hypothesis that trauma is involved in the aetiology of psychosis, is to clarify the underlying mechanism linking trauma and psychosis.

A mechanism through which trauma may impact on the risk for psychosis is sensitisation, a process through which *previous* exposure to adversity or stress makes individuals more sensitive or responsive rather than more resistant to the *later* occurrence of stress (Collip et al. 2008). Previous research has shown that patients with a psychotic disorder are more sensitive for stressors in normal daily life resulting in stronger increases in negative emotions (Myin-Germeys et al. 2001) and psychosis intensity (Myin-Germeys et al. 2005) in reaction to daily life stressors compared with controls. Furthermore, subjects at genetic risk for psychosis (first degree relatives of patients with a psychotic disorder) (Myin-Germeys et al. 2001) and subjects at psychometric risk for psychosis (subjects from the general population who score high on a psychosis proneness scale) (Lataster et al. 2008), also show an increased emotional reactivity to stressors, in comparison with a control group. It is attractive to hypothesize that this increased sensitivity to stress in daily life may be partly the result of a sensitisation process triggered by the experience of earlier childhood trauma. A previous study already demonstrated that a history of serious life events in the past year increases emotional reactivity to stress in patients with a clinically remitted psychotic illness (Myin-Germeys et al. 2003), suggestive of an immediate sensitization process. In addition, it was reported in subjects from the general population that childhood trauma may alter the emotional reaction to daily life stress in adulthood (Glaser et al. 2006). Therefore, the current study aims to investigate the putative association between trauma and psychosis by 1) comparing experiences of trauma in patients with psychosis with a recent onset (<10 years of illness), their siblings, and healthy control subjects, and 2) by investigating the mechanism of sensitization in this sample.

Method

Subjects

A new sample of 50 patients with a recent onset non-affective psychotic disorder (<10 years), was investigated. Also 55 siblings and 45 healthy control subjects were included in the study. Thirty nine sibling were related to the patients participating in the study whereas 16 siblings were unrelated. The CASH (Andreasen et al. 1992) was completed to assess symptom history over the past six months and lifetime, yielding DSM-IV diagnoses (APA 1994). All interviews were conducted by trained research assistants, a clinical/ neuropsychologist (M.L.) and a neuropsychologist (T.L.).

Inclusion criteria for all subjects were: (i) age 18-50 years, and (ii) sufficient command of the Dutch language. Furthermore, patients needed to have a DSM IV diagnosis of a non-affective psychotic disorder as assessed with the CASH (Andreasen et al. 1992) and the first contact with mental health care services had to be less than 10 years ago. Siblings were only included if they had no lifetime history of psychosis, and controls could not have a lifetime nor a family history of psychotic disorder. Patients were recruited through inpatient and outpatient mental health service facilities in the Netherlands and Belgium and siblings were included through their ill relative. The healthy control subjects were recruited through random mailings in the Netherlands and Belgium. Written informed consent, confirming to the local ethics committees guidelines, was obtained from all subjects.

Experience Sampling Method (ESM)

The Experience Sampling Method is a random time-sampling self-assessment technique. Previous applications of ESM in schizophrenia (Myin-Germeys et al. 2001; Delespaul et al. 2002; Myin-Germeys et al. 2002; Myin-Germeys 2009) have demonstrated the feasibility, validity and reliability of using the method in this population. Subjects received a digital wristwatch and ESM assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal at unpredictable moments between 7.30 a.m. and 10.30 p.m. After each 'beep', subjects were asked to stop their activity and fill out the ESM self-assessment forms, collecting reports of thoughts, moods, current context (activity, people present, and location), and severity of symptoms. All self-assessments were rated on 7-point Likert scales.

The ESM procedure was explained to subjects during an initial briefing session and subjects completed a practice form to confirm that they understood the 7-point Likert scales. Subjects were instructed to complete their reports immediately after

the beep, thus minimizing memory distortions, and to record the time at which they completed the form. During the actual sampling period, research staff contacted subjects frequently by phone to assess whether they were complying with the instructions. Finally, the booklets were collected in a short debriefing session. In order to know whether the subjects had completed the form within 15 minutes of the beep, the time at which subjects indicated they completed the report was compared to the actual time of the beep. The subjects were not able to check actual beep times retrospectively. All reports completed more than 15 minutes after the signal were excluded from the analysis. Previous work (Delespaul 1995) has shown that reports completed after this interval are less reliable and, consequently, less valid. Subjects with less than 20 valid reports were also excluded from the analysis (Delespaul 1995).

Childhood Trauma Questionnaire

Childhood trauma was assessed with a Dutch version of the Childhood Trauma Questionnaire 25 item Short Form (CTQ) (Bernstein et al. 1997; Bernstein et al. 2003). The CTQ consisted of 25 questions rated on a 5-point Likert scale enquiring about traumatic experiences in childhood. The CTQ assesses five types of childhood maltreatment: emotional, physical and sexual abuse, and emotional and physical neglect, with five questions per trauma type. A general measure of childhood trauma was generated by calculating the sum of the answers to all 25 questions (range 25-125).

Measures

Previously, emotional stress reactivity was conceptualized as mood reactivity to daily events and minor disturbances in daily life (Myin-Germeys et al. 2001; Myin-Germeys and van Os 2007). Likewise, psychotic stress reactivity in this paper was conceptualized as psychotic reactivity to these daily events. The mood measures, psychosis measures and the stress measures were derived from the experience sampling reports as described below.

Assessment of stress. Stress was conceptualized as subjective appraised stressfulness of small daily events. After each beep subjects were asked to report the most important event that happened between the current and the previous report. This event was subsequently rated on a 7-point Likert scale (-3 = very unpleasant, 0 = neutral, 3 = very pleasant). Responses were recoded to allow high scores to reflect stress (-3 = very pleasant, 0 = neutral, 3 = very unpleasant). The response on this item is called event-related stress.

Activity-related stress: After each beep people were asked to report their activity. Then they were asked to judge this activity with three subsequent questions on a 7-point Likert scale (1 = not at all to 7 = very): *"I would rather do something else", "I am not skilled to do this activity"* and *"This activity requires effort"* (Cronbach's alpha = 0.51). The mean of the answers to these three questions formed the activity-related stress scale.

Assessment of Negative affect. Negative affect (NA) was assessed with the items 'down', 'guilty', 'insecure', 'lonely' and 'anxious' (Cronbach's alpha = 0.84). A mean score of these items was calculated to reflect the amount of NA. To acquire a standardized score this mean score was divided by the standard deviation of the NA score of the total group.

Assessment of psychosis. Psychotic intensity was assessed with 8 ESM items rated on 7-point Likert scales *(1* not at all *to 7* very*)*: *"My thoughts are now paranoid", "My thoughts are difficult to express", "I can't get rid of my thoughts", "My thoughts are influenced by other people", "I'm suspicious", "I feel unreal", "I see things", "I am afraid to do something uncontrolled"* (Cronbach's alpha = 0.76). The use of these items to reflect psychotic psychopathology has been validated previously (Delespaul 1995; Delespaul et al. 2002; Myin-Germeys et al. 2005; Myin-Germeys et al. 2005). A sumscore of these 8 items was calculated and this score formed the variable psychopathology.

Analyses

1) Is trauma associated with vulnerability for psychosis?
Oneway ANOVA tests with posthoc Bonferroni tests were conducted to assess differences in in trauma levels, as well as differences in clinical and demographic characteristics between the three groups.

2) Is trauma associated with increased sensitivity to stress?
In order to investigate the association between childhood trauma and stress reactivity, a multilevel linear random regression model was used. Multilevel or hierarchical linear modelling techniques are a variant of the more often used unilevel linear regression analyses and are ideally suited for the analysis of the nested ESM data. ESM data have a hierarchical structure as multiple observations (level 1) are nested within subjects (level 2). In ESM, observations from the same subject are more similar than observations from different subjects. Therefore, the residuals are not independent. Conventional regression techniques do not take the variance components at two different levels into account. Data were therefore analyzed using the XT-

MIXED multilevel random regression routine in STATA (StataCorp 2001). The β's are the fixed regression coefficient of the predictor in the multilevel model and can be interpreted identically to the estimate in a unilevel linear regression analysis (i.e. change in dependent variable with one unit change in the independent variable).
In order to test the hypothesis that trauma is influencing the emotional or psychotic reaction to daily life stress, regression analyses were conducted with standardized NA (defined as NA/SD of NA over the whole sample) and standardized psychosis (defined as psychosis/SD of psychosis over the whole sample), respectively, as the dependent variables and the main effects of trauma and stress and their two-way interaction as the independent variables (general model: NA/ psychosis = β0 + β1trauma + β2stress + β3trauma x stress + residual). Finally, posthoc analyses were used to estimate effect sizes of stress stratified by high versus low trauma using the STATA LINCOM routine.

Results

Subjects and descriptives

The final sample included 150 participants: 50 patients, 55 siblings and 45 controls. Of the sample, 5 subjects (1 patient, 2 siblings and 2 controls) did not complete the PANSS questionnaire. Therefore, for these subjects, no data was available on symptomatology during the ESM week. Sociodemographic and clinical characteristics of the final sample are summarized in table 1.

Is trauma associated with vulnerability for psychosis?

Group was significantly associated with trauma level ($F(df=2)=8.66$, $p<0.001$). The patients (M= 41.1 (SD=11,2) reported significantly more trauma compared to the siblings (M=34.3 (SD=7.8) and controls (M=33.6 (SD=10.4), the latter two did not differ from each other. When trauma was dichotomized into a high trauma category (> 90 percentile) and a low trauma category (<90 percentile), 20% (n=10) of the patients belonged to the severe trauma category compared to only 4% (n=2) and 7% (n=3) of the siblings and controls.

Table 1: Sociodemographic and clinical characteristics of the research sample.

	Patients (n=50)	Siblings (n=55)	Control Subjects (n=45)
Age (M (SE); range)	26.2 (6.7); 17-45	25.4 (6.6); 16-45	32.2 (10.2); 16-49
Sex (M - F)	35 – 15	24- 31	13 - 32
Education			
Elementary school	0%	0%	0%
Secondary school	75%	49%	38%
Higher education	25%	51%	62%
Marital Status			
Married or living together	16%	35%	60%
Divorced	2%	0%	7%
Never married	82%	65%	33%
Work situation			
Household	2%	2%	2%
Education	14%	42%	25%
Working	12%	49%	71%
Reintegrating		2%	0%
Unemployed	20%	5%	2%
Incapable to work	50%	0%	0%
Protected work	2%	0%	0%
CASH DSM-IV Axis I diagnosis lifetime (n)			
Depressive disorder	-	8	7
Schizophrenia	31	-	-
Schizoaffective disorder	7	-	-
Schizophreniform disorder	1	-	-
Brief psychotic disorder	1	-	-
Delusional disorder	2	-	-
Psychotic disorder NAO	8	-	-
No disorder	-	47	38
Illness duration of the psychotic disorder in months (M (SE); range)	43.3 (31.4); 1-169	-	-
Total PANSS score (M (SE); range)	1.7 (0.5); 1-3.6	1.1 (0.1); 1-1.6	1.1 (0.2); 1-2
PANSS Positive symptoms (M (SE); range)	1.8 (0.7); 1-3.7	1.1 (0.1); 1-1.4	1.1 (0.2); 1-2
PANSS Negative symptoms (M (SE); range)	1.7 (0.9); 1-5.4	1.1 (0.2); 1-1.7	1.1 (0.2); 1-2

Emotional sensitization to daily life stress

Since trauma was clearly correlated with patient-status, no interaction effect could be fitted between trauma, group and stress on the outcome variable. In addition, the low levels of trauma in the siblings and control groups precluded examination of sensitization in these groups. Therefore, sensitization was studied in the patient group only. Of the individuals in the patient group, 3 participants were unable to comply with the research protocol (they filled in fewer than 20 valid reports) and were therefore excluded from the analyses. The final ESM patient sample thus consisted of 47 patients. The number of valid reports and the mean scores on the dependent and independent variables of the patient group are shown in table 2.

Table 2. Means and standard deviations of the valid reports and the dependent and independent ESM variables in the patient group (n=47)

	Mean	SD
Valid ESM reports	39.1	9.3
NA	1.81	0.84
Psychosis	1.52	0.62
Event-related stress	- 1.38	0.80
Activity-related stress	2.57	0.70

In order to investigate severe trauma, trauma was dichotomized into a severe trauma patient group (>90th percentile) and a no severe trauma patient group (<90th percentile).
Multilevel random regression analyses showed a main effect of event-related and activity-related stress in the model of NA (event-related stress: $\beta = 0.09$ (SE = 0.01), $p<0.001$; Activity-related stress: $\beta = 0.12$ (SE = 0.01), $p<0.001$)). No main effect of severe trauma was found in the model predicting NA ($\beta = 0.03$ (SE = 0.39), $p = 0.93$). However, a significant interaction was found between severe childhood trauma and event-related stress ($\beta = 0.12$ (SE = 0.03), $p<0.001$), indicating that a history of severe trauma increased emotional reactivity to daily stress. A similar interaction effect was found between activity-related stress and severe trauma in the model predicting NA ($\beta = 0.15$ (SE = 0.05); $p<0.01$). Stratified analyses are shown in table 3.

Psychotic sensitization to daily life stress

Multilevel random regression analyses showed that there was a main effect of event-related and activity-related stress in the model of psychopathology (event-related stress: $\beta = 0.07$ (SE = 0.01), $p<0.001$; activity-related stress: $\beta = 0.10$ (SE = 0.01), $p<0.001$)). However, no main effect of severe trauma was found, although there appeared to be a trend ($\beta = 0.70$ (SE = 0.38), $p = 0.07$). Again, a significant

interaction effect was found between childhood trauma and stress in the model predicting psychosis (event-related stress: β = 0.17 (SE = 0.03), p<0.001; activity-related stress: β = 0.32 (SE = 0.05), p<0.001). Again, stratified analyses are shown in table 3.

Table 3. Effect sizes of event-related and activity-related stress on NA and psychosis respectively for the low trauma and high trauma patient groups

	Low trauma β (SE); p	High trauma β (SE); p
NA		
Event-related stress	0.08 (0.01), p<0.001	0.20 (0.03); p<0.001
Activity-related stress	0.11 (0.02), p<0.001	0.26 (0.05), p<0.001
psychosis		
Event-related stress	0.05 (0.01), p<0.001	0.23 (0.03), p<0.001
Activity-related stress	0.08 (0.01), p<0.001	0.41 (0.05), p<0.001

Discussion

The results of this study show that 1) patients report significantly higher levels of childhood trauma compared to siblings and controls, and 2) experiences of trauma during childhood in patients are associated with stronger emotional and psychotic reactions to small daily stressors. These findings support the sensitization hypothesis suggesting that exposure to severe stressors during childhood may increase sensitivity to smaller stressors later in life. The effect sizes were small but not negligible, especially since we assessed frequently occurring exposures in daily life, the cumulative effects of which may be considerable.

Trauma and psychosis

The current paper demonstrates a clear association between trauma and psychosis as childhood trauma was significantly higher in the patient group in comparison with the siblings of patients with a psychotic disorder and a healthy control group. This is in line with previous findings of an association between trauma and clinical and sub-clinical psychosis (Read et al. 2005; Spauwen et al. 2006; Kelleher et al. 2008). Two recent reviews suggested that the lack of appropriate control groups, the chronic patient samples and the measurement of trauma were important flaws in previous patient studies, limiting the conclusions with regard to the putative association between trauma and psychosis (Morgan and Fisher 2007; Bendall et al. 2008). The current study used healthy volunteers selected through random mailings as well as a genetically high risk group (siblings of the patient group) as controls. In

addition, the patient group was a recent onset group with an illness duration of less than 10 years. Finally, the CTQ, "a validated trauma measure that include objective-specific questioning of child physical, sexual and emotional abuse and neglect" (Bendall et al. 2008) was used to measure trauma. The results of the current study, thus, seem to provide further evidence for an association between trauma and psychosis.

The finding that siblings of patients with psychosis do not differ from controls in exposure to trauma may be surprising, as it could be expected that siblings would share at least some traumatic experiences. These data may thus provide support for a recall bias. Patients suffering from psychosis may tend to overreport exposure to trauma in their childhood; a post-hoc analysis indeed indicated little overlap between trauma levels in patients and their relatives in (B=0.11 (SE = 0.11), p=0.31). However, harsh parental behaviour directed at one person in the family may have protective effects for other children in the family, a phenomenon called the 'sibling barricade'(Reiss et al. 1995). It is therefore possible that patients but not their siblings experienced trauma in the shared family environment.

Alternatively, low trauma levels in subjects who are vulnerable for psychosis, yet did not develop a psychotic disorder, may represent a plausible explanation for the observed sibling discordance. If trauma truly is an etiological factor in the onset of psychosis, subjects at genetic risk for psychosis would have made a transition to psychosis when exposed to trauma. They would have become patients, whereas the absence of severe childhood trauma might have protected the healthy relatives from developing a psychotic disorder.

The sensitization hypothesis

The current findings support the hypothesis that exposure to trauma in the patient group is associated with a sensitized state in adulthood characterized by elevated emotional and psychotic reactions to small daily life stress. This is in line with findings from a previous study which demonstrated that a history of serious life events in the past year increased emotional reactivity to stress in patients with a clinically remitted psychotic illness (Myin-Germeys et al. 2003). It also extends findings from general population studies that found altered emotional reactivity to daily life stress in adulthood after exposure to childhood trauma (Glaser et al. 2006).

These findings provide further evidence at the behavioural level for the hypothesis that sensitization may provide a plausible mechanism for the putative link between environmental exposures and the development of psychosis (Collip et al. 2008). It also fits with the notion of an independent affective pathway to psychosis, which is characterized by increases in psychotic and emotional reactivity to stress, possibly

induced by major stressful events such as childhood trauma or life events (Myin-Germeys and van Os 2007).

The process of behavioural sensitization may also be reflected at the biological level. Exposure to trauma has been found to alter the HPA-axis, which is one of the major systems involved in the stress-response. One study showed that exposure to childhood trauma may increase the activity of the HPA-axis in adulthood (Heim et al. 2000), whereas another study reported dysregulated HPA-axis functioning in sexually abused girls (De Bellis et al. 1994). Interestingly, increased HPA-axis activity has also been associated with psychosis (van Winkel et al. 2008; Walker et al. 2008). Elevated baseline cortisol and adrenocorticotropic hormone levels have been found in patients with psychosis, as well as an increased cortisol response to a pharmacological stressor (van Winkel et al. 2008; Walker et al. 2008). In addition, illnesses that are associated with elevated cortisol levels (eg Cushing syndrome), but also the administration of corticosteroids, can induce psychotic symptoms (van Winkel et al. 2008; Walker et al. 2008). Furthermore, marked reductions in the volume of the hippocampus, a brain region that plays an important role in the feedback mechanism of the HPA axis, have been reported (van Winkel et al. 2008; Walker et al. 2008).

Childhood trauma may also affect dopaminergic transmission, which has been implicated in the development of psychosis. It has been suggested that psychosis is associated with mesolimbic dopamine sensitization characterised by a hyperreactivity of dopamine (DA) neurons to environmental stimuli, with even exposure to moderate levels of stress being associated with an excessive DA response (Laruelle 2000). This has been reported in animal studies which have shown that negative and threatening events can produce dopaminergic hyperactivity in the mesocorticolimbic system (Hall et al. 1999). Furthermore, it was shown that prolonged exposure to aversive environments can lead to sensitisation of the dopaminergic system (Tidey and Miczek 1996). In humans, elevated dopamine levels were found in girls who had been sexually abused in comparison with non-abused controls (De Bellis et al. 1994). Another study showed that a psychosocial stress task caused a significant release of dopamine, especially in individuals who had experienced low maternal care, suggesting a sensitization effect (Pruessner et al. 2004). Interestingly, Walker and Diforio (Walker et al. 2008) suggested a synergistic relation between activation of the HPA axis and activation of dopaminergic circuits, with glucocorticoid secretion increasing dopamine activity in certain brain regions, in particular the mesolimbic system. Increased dopamine activity may then lead to the emergence of psychotic symptoms. Kapur (2003) suggested that a dysregulated, hyperdopaminergic state may cause stimulus independent release of dopamine, which may take over the normal process of contextually driven salience attribution and leads to aberrant assignment of salience to external objects and internal representations.

Clinical implications

This paper demonstrated that childhood trauma may be associated with psychosis, possibly through a mechanism of sensitization. Clearly, these results are still a long way from offering direct therapeutic insight. However, if stress-sensitivity is a mechanism underlying the association between trauma and the development of psychosis, it may be important to tailor treatment aimed at reducing sensitivity to stress in daily life. One possible way to do so is by reducing stress in the social environment of the patient, possibly by teaching people how to use self-relaxation or distraction techniques. Hodel et al. (Hodel et al. 1998) showed that this improves emotional well-being in patients with schizophrenia with a chronic illness course but not in early psychosis. Another possibility is to use Cognitive Behavioural Therapy (CBT) to remediate stress-sensitivity. Previous studies have shown that Cognitive Behavioural Therapy (CBT) reduces psychotic symptoms (Pilling et al. 2002) and reduces distress caused by psychotic symptoms (Valmaggia et al. 2005). Furthermore, in a recent study it was found that CBT has beneficial effects on depression at 24 months follow up, as well as on delusional distress and social functioning, but there was no effect on the risk of relapse (Garety et al. 2008). Birchwood and Trower (Birchwood and Trower 2006) also proposed that CBT should focus primarily on the emotional dysfunction in psychosis rather than focus on the improvement of the psychotic symptoms. It may be useful to extend the therapy in such a way that treatment also focuses on emotional sensitivity to stress in daily life.
In addition, it may be important to prevent the process of sensitization in the earliest initial phase. The prospective study by Spataro et al. (Spataro et al. 2004) found no association between childhood trauma and the later development of psychosis. One possible explanation of this failure to find an association is that the included cases were derived from police or other official reports. These children were thus recognised as being a victim of trauma and possibly received treatment, which may have prevented or reversed the sensitization process.

Limitations

The results of this paper should be interpreted in the light of several potential limitations.
The ESM measurements of negative affect, psychopathology and daily life stress are based on subjective reports. Although subjective reports are considered less reliable (e.g. do all subjects interpret or answer the questions identically?), they can be valid whereas the validity of objective approaches should not be taken for granted (Strauss 1994).

Second, there was one patient who had an illness duration of more than 10 years. However, posthoc analyses without this patient did not change the results significantly.
Third, the present study was a cross-sectional study, which makes it impossible to establish causal relationships. Therefore it is impossible to determine whether stress measures influenced psychosis, or psychosis influenced the subjective appraisal of stress. However either explanation has clinical relevance.
Finally, the current study used ESM, a daily life assessment technique in which subjects have to comply with a paper-and-pencil diary protocol without the researcher being present. Recently, some authors have put doubt on subject reliability and compliance in paper-and-pencil ESM studies, favoring the use of electronic devices (Stone et al. 2002). However, in a comparative study, Green et al. concluded that both methods yielded similar results (Green et al. 2006). In addition, a recent study of our group using a signal-contingent random time sampling procedure with multiple observations per day - such as the protocol used in the current study – also found evidence underscoring the validity of the paper-and-pencil random time self-report data in the current study (Jacobs et al. 2005).

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Chapter 3

Stress and cortisol in subjects at risk for psychosis: an experience sampling study

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Abstract

Background: First-degree relatives of patients with a psychotic disorder react with subtle increases in non-clinical psychotic experiences when faced with stress. The current study investigated to what degree these behavioural changes are predicted by changes in the hypothalamic-pituitary-adrenocortical axis, as indexed by cortisol level.

Methods: The sample consisted of siblings of patients with a psychotic disorder (n = 58) and healthy control subjects (n = 62). The Experience Sampling Method (ESM; a structured diary technique) was used to assess stress and psychotic experiences in daily life and to sample salivary cortisol levels.

Results: Multilevel analyses revealed higher diurnal cortisol level and heightened cortisol to stress in siblings compared to controls. Diurnal cortisol slope did not differ between the two groups, but transient deviations from an individual's modelled cortisol curve significantly predicted increases in intensity of subclinical psychotic experiences, particularly in the sibling group.

Conclusions: The findings are compatible with HPA axis overactivity in individuals at genetic risk for psychosis. The data suggest an association between increased cortisol reactivity and the intensity of psychotic-like experiences, although the direction of this association remains to be elucidated.

Key words: Psychosis, cortisol, HPA axis, experience sampling, siblings, daily stress

Introduction

Psychosis may be viewed as an abnormal reaction to stress in the form of delusions and hallucinations (Myin-Germeys et al. 2005). Evidence for psychotic reactivity to daily stress has been observed in patients diagnosed with a psychotic disorder as well as in their healthy first-degree relatives, who are genetically at risk to develop psychosis (Myin-Germeys et al. 2001). However, the biological substrate underlying this phenomenon remains largely unknown. Increased psychotic reactivity to stress has been related to increased dopamine reactivity in first-degree relatives of patients (Myin-Germeys et al. 2005; Soliman et al. 2008). However, it is also plausible that the hypothalamic-pituitary-adrenocortical (HPA) axis plays a role, given the sensitivity of this neuroendocrine system to stressors (Walker and Diforio 1997; Corcoran et al. 2001). Several lines of evidence suggest an association between HPA axis activity and psychotic experience (van Winkel et al. 2008). Elevated diurnal cortisol levels have been found in patients with a psychotic disorder (Ryan et al. 2004; Walsh et al. 2005), as well as an increased cortisol response to a pharmacological challenge (Walker and Diforio 1997; Elman et al. 1998). However, other studies have found blunted stress responses in patients with psychosis (Albus et al. 1982; Breier et al. 1988; Jansen et al. 1998; Jansen et al. 2000; Marcelis et al. 2004; Brenner et al. 2009) and with schizotypal personality disorder (Mitropoulou et al. 2004).

Most research has investigated cortisol levels in patients receiving antipsychotic medication, which may itself influence cortisol levels (Meltzer 1989; Wik 1995). The current study therefore focuses on cortisol patterns in siblings of patients, because they show stress-related increases in subtle psychotic experiences similar to those observed in patient populations (Myin-Germeys et al. 2005) but are at the same time medication-free. By investigating cortisol reactivity in everyday contexts the current study can help clarify the importance of small stresses in daily life in the development of psychotic disorder (Norman and Malla 1991; Myin-Germeys et al. 2001).

First, cortisol levels and the diurnal pattern (slope) of cortisol secretion were examined in siblings and healthy controls. Second, we tested for differences between siblings and controls in cortisol reactivity to naturally occurring stressors. Finally, the study examined the extent to which within-person fluctuations in cortisol were associated with transient increases in subclinical psychotic experiences.

Methods and materials

Participants

The sample consisted of 72 healthy siblings (69 full siblings and 3 half siblings) of patients diagnosed with a psychotic disorder and 66 control subjects. Inclusion criteria were: (1) age 18-50 years; (2) sufficient command of the Dutch language. Exclusion criteria were: (1) use of steroid medication; (2) current axis 1 disorders; (3) lifetime history of psychotic disorder; and for the controls (4) family history of psychotic disorder. Exclusion criteria 2 through 4 were assessed with the interview Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992). Written informed consent, conforming to the local ethics committee's guidelines, was obtained from all subjects.

Experience Sampling Method (ESM)

The Experience Sampling Method is a random time-sampling self-assessment technique. The feasibility, validity and reliability of ESM have been demonstrated (Myin-Germeys et al. 2001; Delespaul et al. 2002; Myin-Germeys et al. 2002; Myin-Germeys in press). Subjects received a digital wristwatch which emitted a signal, ten times a day on six consecutive days at unpredictable moments between 7:30 a.m. and 10:30 p.m. After each 'beep', subjects were asked to fill out the ESM self-assessment forms concerning current thoughts, moods, context, and psychotic experiences. All self-assessments were rated on 7-point Likert scales. Subjects were instructed to complete their reports immediately after the beep, thus minimizing memory distortions, and to record the time at which they completed the form. All reports completed more than 15 minutes after the signal were excluded from the analysis. Subjects with fewer than 20 valid reports were also excluded from the analysis.

Cortisol collection

At each ESM beep, subjects also collected a saliva sample with a cotton swab (Salivette; Sarstedt, Etten-Leur, the Netherlands). Subjects were instructed to store the used swab in the salivette tube and to record the exact time of collection on the label. Samples were stored in subjects' home freezers until transport to the lab, where uncentrifuged samples were kept at -20°C until analysis.

Measures

Assessment of daily stress. Stress was conceptualized as subjectively appraised unpleasantness of small daily events. After each beep, subjects were asked to report the most important event that had happened between the current and the previous report. The valence of this event was then rated on a 7-point Likert scale and recoded to allow high scores to reflect stress (-3 = very pleasant, 0 = neutral, 3 = very unpleasant).

Assessment of psychotic experiences. Psychotic symptomatology was assessed with 8 ESM items rated on 7-point Likert scales (1 = not at all to 7 = very), such as "My thoughts are now paranoid", "My thoughts are difficult to express", "I'm suspicious", "I see things" (Cronbach's alpha = 0.67). The use of these items to reflect psychotic psychopathology has been validated previously (Myin-Germeys et al. 2005). The mean score of these 8 ratings formed the variable *psychotic experiences*.

Salivary cortisol. Salivary cortisol is a valid, reliable and non-invasive measure of the free, unbound cortisol in blood, which is considered to be the biologically active hormone. A radioimmunological procedure (Department of Reproductive Physiology, School of Veterinary Medicine, University of Liège) was performed in duplicate on 50 µl of saliva in competition with a tracer solution of cortisol-3CMO coupled with 2-[^{125} I] histamine and for specific antibodies raised against cortisol-3CMO-BSA (Sulon et al. 1978). The lower detection limit of the assay was 0.2 nmol/L. The intra- and inter-assay coefficients of variation were < 5% and <12%, respectively. All samples from an individual were analyzed in the same assay to reduce sources of variability. Cortisol values more than four standard deviations above the grand mean were considered abnormal; 463 observations were deleted because they exceed this cutoff. Raw cortisol values were log transformed to reduce skewness of distribution (Peeters et al. 2004), generating the variable lncort. The variable time was centered around the grand mean for all samples (Peeters et al. 2004).

Analyses

T-tests were conducted to investigate group differences in number of valid ESM reports, mean ratings of psychotic experiences and event-related stress. To analyze the ESM and cortisol data, we used multilevel regression techniques, which take the hierarchical structure of the data (observations nested within subjects) into account. Thirty-five families provided more than 1 participant, resulting in a third level (family). Data were therefore analyzed using the XTMIXED multilevel random regression routine in STATA (StataCorp 2001). The B's are the fixed regression coefficients of the predictors in the multilevel model. In all analyses with lncort as

dependent variable, a fourth-degree polynomial of the variable time was added to account for the diurnal pattern of cortisol (Peeters et al. 2004). Further, the analyses were corrected for the following *a priori* confounders: gender, age, recent consumption of food or alcohol, recent tobacco use and use of oral contraceptives.

Diurnal cortisol patterns
To test whether mean cortisol level differed between the two groups, a regression analysis was conducted with lncort as the dependent variable and the categorical variable group (0 = controls, 1= siblings) as the independent variable. In addition, time of day (linear component) and a group by time interaction were added as independent variables to examine the effect of group on the diurnal cortisol slope.

Cortisol reactivity to daily stress
To investigate whether stress elicited differential cortisol reactions in the two groups, a multilevel analysis was conducted with lncort as the dependent and group, event-related stress and their interaction as the independent variables.

Changes in cortisol in relation to psychotic experiences
To examine whether within-person fluctuations in cortisol were associated with increases in psychotic experiences, we first fitted a daily cortisol pattern for each person controlling for the previously mentioned confounders. We then estimated deviations in cortisol from this predicted curve, using the post-estimation command PREDICT (residuals) in STATA (StataCorp 2001). This procedure calculates residuals, which are equal to the responses minus the fitted values. The fitted values take into account random effects from all levels in the model (StataCorp 2001). In a second analysis, we additionally controlled for negative affect since negative emotions have been associated with both cortisol and psychosis (Myin-Germeys et al. 2001; Freeman and Garety 2003; Thompson et al. 2007).

A multilevel analysis was then conducted with psychotic experiences as the dependent variable and group, the predicted cortisol residuals, and the interaction between group and the cortisol residuals as the predictors. To clarify group differences in the case of significant interaction, stratified analyses were conducted with the STATA LINCOM command, calculating the appropriate linear combinations from the model including the interaction term.

RESULTS

Compliance and sample characteristics

Eighteen participants (14 siblings and 4 control subjects) were unable to comply with the research protocol (13 of them filled in fewer than 20 valid reports and 5 had extremely high cortisol values) and were therefore excluded from the analyses. The final sample included 120 participants: 58 siblings and 62 controls. These subjects together yielded 5057 ESM observations, with a mean of 45.2 ESM observations per subject. Socio-demographic characteristics of the final sample are summarized in Table 1. The number of valid reports and the mean scores on the independent variables are shown in Table 2.

Table 1. Sample characteristics

	Siblings (n = 58)	Control Subjects (n = 62)
Age (mean; range)	29; 16-54	33; 16-57
Sex (M / F)	20 / 38	17 / 45
Education		
Elementary school	2%	2%
Secondary school	46%	32%
Higher education	52%	66%
Marital status		
Married or living together	52%	61%
Divorced	2%	7%
Never married	46%	32%
Work situation		
Household	2%	3%
Student	33%	21%
Working	61%	71%
Unemployed	4%	2%
Work disability	0%	3%
CASH[1] DSM-IV Axis I diagnosis lifetime (n)		
Depressive disorder	11	10
No disorder	47	52

[1]Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992)

Table 2. Means[1], standard deviations and T-test statistics of the valid reports and Experience Sampling variables

	Siblings (n = 58) Mean (SD)	Controls (n = 62) Mean (SD)	T	p
Valid reports	41.0 (9.4)	45.4 (8.4)	2.71	0.008
Psychotic experiences	1.11 (0.17)	1.10 (0.16)	-0.23	0.820
Event-related stress	1.33 (0.28)	1.42 (0.35)	1.49	0.138

[1] For each subject, a mean was calculated over all reports, and these means were then aggregated over each group to obtain the group mean and SD.

Diurnal cortisol patterns

Siblings had significantly higher diurnal cortisol levels than controls (B=0.17, SE=0.07, p=0.020). No difference in cortisol curve between siblings and controls was found (B=-0.01, SE=0.003, p=0.125). Cortisol curves (raw data) for both groups are shown in Figure 1.

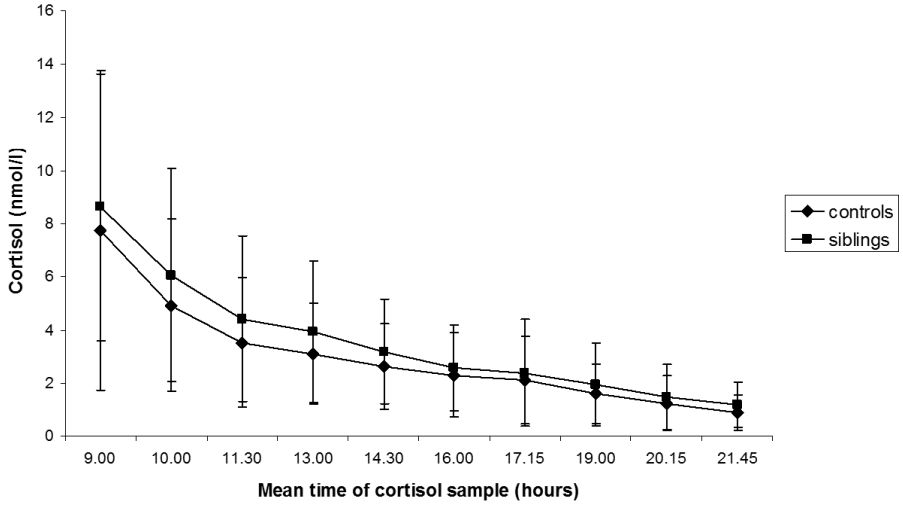

Figure 1. Diurnal cortisol curves of the siblings (n = 58) and the control group (n = 62). On the x-axis are the mean beep times of the experience sampling method reported. For every beep the mean cortisol value was calculated for the two groups. The error bars indicate the standard deviations of the cortisol values per beep.

Cortisol reactivity to daily stress

Multilevel analysis revealed no main effect of daily stress on cortisol (B=0.001, SE=0.005, p=0.83). However, there was a significant interaction between group and stress (B=0.02, SE=0.01, p=0.05), with the genetic risk group (siblings) displaying a stronger cortisol response to stress.

Intraindividual cortisol fluctuations in relation to psychotic experiences

Increases from the modelled individual diurnal cortisol curves were a significant predictor of transient increases in psychotic experiences (B=0.01, SE=0.01, p=0.026). The interaction between group and predicted residuals from the cortisol curve was statistically significant (B=0.04, SE=0.01, p=0.002), with deviations from the individually estimated curve being associated with increases in psychotic experiences in siblings (B=0.03, SE=0.01, p=0.001) whereas no such effect was found in the controls (B=-0.004, SE=0.01, p=0.67).
When additionally controlling for negative affect, the effect sizes slightly decreased, but remained significant.

DISCUSSION

The results show that individuals with a genetic risk for psychotic disorder, by virtue of being siblings of patients with this diagnosis have higher mean cortisol levels and greater cortisol reactivity to daily stress than healthy control subjects. Intensity of psychotic experiences was related to transient increases in cortisol secretion, and this effect was more pronounced in subjects at genetic risk for psychosis. The effect sizes were small but not negligible, especially since we assessed frequently occurring exposures in daily life, the cumulative effects of which may be considerable.

Methodological issues

The results of this paper should be interpreted in the light of several potential limitations.
The ESM measurements of psychopathology and daily life stress are based on subjective reports. Although subjective reports are considered less reliable (e.g. do all subjects interpret or answer the questions identically?), they can be valid whereas the validity of objective approaches should not be taken for granted (Strauss 1994).
Recently, some authors have put doubt on the reliability and subject compliance in paper-and-pencil ESM studies, favoring the use of electronic devices (Stone et al.

2002). However, in a comparative study, Green *et al.* (2006) concluded that both methods yielded similar results (Green et al. 2006). In addition, a recent study by our group using a signal-contingent random time sampling procedure with multiple observations per day - such as the protocol used in the current study – also found evidence underscoring the validity of the paper-and-pencil random time self-report data in the current study (Jacobs et al. 2005). Furthermore, inclusion of non-compliant cortisol samples did not distort the diurnal cortisol curve (Jacobs et al. 2005).

Diurnal cortisol patterns

The finding that people at genetic risk for psychosis show higher cortisol levels than healthy control subjects extends previous reports of elevated cortisol in patients with psychosis (Muck-Seler et al. 2004) and suggests that hyperactivity of the HPA axis may be a marker for familial and possibly genetic risk for psychotic disorder (Weinberger 1999). It has been suggested that these elevated cortisol levels in psychotic patients and their siblings reflect disturbances in the negative feedback regulation of the HPA axis (Phillips et al. 2006). This notion fits with previous findings of reduced hippocampal volume in schizophrenia patients (Wright et al. 2000), as the hippocampus plays a role in dampening HPA axis activity (van Winkel et al. 2008).

Cortisol, stress and psychosis

The results of the current study show that individuals at risk show heightened cortisol reactivity to stress, compared to healthy controls. Previous studies investigating cortisol reactions to stress in psychosis have shown mixed results. Several studies investigating a psychological stressor, such as a public speaking task, in patients with a psychotic disorder have shown a blunted cortisol response (Albus et al. 1982; Breier et al. 1988; Jansen et al. 1998; Jansen et al. 2000). One study investigating cortisol response after a physical stressor found no difference between patients and healthy controls (Jansen et al. 2000), whereas studies investigating pharmacological stressors have shown mixed results, with both increased (Walker and Diforio 1997; Elman et al. 1998) and blunted (Marcelis et al. 2004; Mitropoulou et al. 2004; Brenner et al. 2009) cortisol responses. There are two limitations in previous studies investigating cortisol reactivity. First, most studies examined patients taking antipsychotic medication, which can confound cortisol levels (Meltzer 1989; Wik 1995). Second, almost all previous studies have investigated cortisol in response to a laboratory stressor. The current study investigated smaller stressors occurring in the realm of daily life in a sample of unmedicated siblings. To our knowledge, there is only one previous study investigating the association between hassles and cortisol

levels in an ultra high risk group; this study reported that plasma cortisol levels were significantly and positively correlated with the experience of daily hassles (Thompson et al. 2007), which is in line with the current findings.

Is cortisol associated with psychotic experiences?

An interesting finding of the current study is that momentary deviations from estimated individual cortisol curves were associated with increases in psychotic symptomatology. Since we used cross-sectional analyses assessing psychotic experiences and cortisol at the same time, the results could be interpreted in two directions. It could suggest that alterations in cortisol may be involved in the pathogenesis of psychotic experiences. Previously, it has been hypothesized that there is a synergistic relation between activation of the HPA axis and activation of dopaminergic circuits implicated in psychosis (Walker and Diforio 1997). Evidence suggests that glucocorticoid secretion may increase dopamine activity in certain brain regions, in particular the mesolimbic system (Walker et al. 2008), which has been implicated in the pathogenesis of positive psychotic experiences. The finding that heightened cortisol levels may cause elevated dopamine levels (Marinelli and Piazza 2002) then suggests that heightened cortisol levels may also result in more psychotic experiences as suggested by the findings of the current study.
Alternatively, however, one could hypothesize that the distress associated with the psychotic experiences increases cortisol levels. Several studies have shown that psychotic experiences are related to increases in anxiety, negative affect and distress (Myin-Germeys et al. 2001; Freeman and Garety 2003), whereas negative affect has been suggested to drive cortisol increases (van Eck et al. 1996; Smyth et al. 1998; Hanson et al. 2000; Jacobs et al. 2007). This would also fit with the findings of Thompson *et al.* (2007) who found increased cortisol reactions to daily hassles to be associated with anxiety and depression, but not psychosis in subjects at ultra-high risk for psychosis. However, they were using retrospective questionnaires to assess daily hassles rather than investigating prospectively the immediate psychotic reactions to daily stress. When we added negative affect as a confounder in the model, the interaction effect reduced but remained significant. This suggests that psychosis induced negative affect increasing cortisol levels is unlikely to be the sole explanation for the association between cortisol deviations and increased psychotic experiences.

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Chapter 4

The dynamics of symptomatic and non-symptomatic coping with psychotic symptoms in the flow of daily life

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Abstract

Introduction: Previous research has suggested that going along with psychotic symptoms (symptomatic coping) is less effective than other coping strategies with psychotic symptoms. This pilot study aims to validate such findings using a momentary assessment strategy of coping with stress in daily life.
Method: Patients with psychosis (n=35) were studied with the Experience Sampling Method (ESM; a structured diary technique) to assess coping with stress in daily life. This was analysed in relation to coping with psychotic symptoms using a previously validated interview (Maastricht Assessment of Coping Strategies).
Results: Symptomatic and Non-symptomatic Coping were negatively associated with each other. Symptomatic Coping was negatively associated with the level of coping in daily life, whereas a positive association was apparent for Non-symptomatic Coping. Non-symptomatic Coping, but not Symptomatic Coping, predicted appraisals of distress associated with psychotic symptoms.
Conclusion: Effective coping may be associated with the tendency to develop conscious appraisals of distress associated with psychotic symptoms.

Keywords: Psychosis; Coping; MACS; Experience Sampling Method

Introduction

Several studies have shown that individuals suffering from psychosis try to control their symptoms using various coping strategies (Falloon and Talbot 1981; Romme et al. 1992; Middelboe and Mortensen 1997; Boschi et al. 2000). One of these is symptomatic behaviour or going along with the symptoms (e.g. following orders from voices or keeping a knife ready to defend oneself against an imagined persecutor) (Carr 1988). Previous research has shown that symptomatic coping is most frequently used in patients with psychosis, although it is reported to be a less effective coping strategy than the other forms of non-symptomatic coping (Bak et al. 2001; Bak et al. 2003). Beyond the above findings, however, not much is known about the dynamics of symptomatic versus non-symptomatic coping with psychotic symptoms, in particular as coping is typically assessed in the traditional psychometric fashion: retrospectively using a single cross-sectional interview.

It can be hypothesised that the difference between symptomatic and non-symptomatic coping may lie in differences in the degree to which psychotic symptoms generate conscious appraisals of distress. For example, a person may have the delusional idea that someone wants to harm him or her. The difference between carrying a weapon to defend him- or herself (symptomatic coping) or develop non-symptomatic coping in the form of, for example, finding distraction, may be related to the degree in which the person develops a conscious appraisal of actually being distressed by the experience itself. If this mechanism differentiated between symptomatic and non-symptomatic coping, one would expect high levels of symptomatic coping, assessed retrospectively, to be associated with i) less distress in relation to psychotic symptoms and ii) less coping assessed prospectively. Therefore, the aim of this study was to test these two hypotheses. As the two hypotheses implicitly assume that some patients habitually tend to use more symptomatic coping whereas other patients habitually use more non-symptomatic coping, the additional hypothesis was tested that there is a negative association between symptomatic and non-symptomatic coping.

Methods

Subjects

The sample consisted of 35 outpatients with a diagnosis of schizophrenia, assigned by the treating psychiatrist according to DSM-IV criteria using the Brief Psychiatric Rating Scale (Ventura et al. 1993) to map psychiatric symptomatology (see (Morrens et al. in press) for further description of the sample). Written informed consent,

conforming to the local ethics committee's guidelines, was obtained from all subjects. Nine subjects were unable to comply fully with the research protocol (see ESM procedure). The final sample included 26 patients (17 males and 9 females) with a mean age of 37.9 (SD = 11.2).

Experience Sampling Method (ESM)

The ESM is a random time-sampling self-assessment technique (Delespaul 1995; Myin-Germeys et al. 2001). The subject is signaled by a digital wristwatch ten times a day on 6 consecutive days at unpredictable moments between 7.30 AM and 10.30 PM. After each signal (a beep), the subject is asked to fill in a form asking about current thoughts, mood, context, severity of symptoms and coping with stress. All questions are presented as 7-point Likert scales. Only reports within a range of 5 minutes before until 15 minutes after the beep were used, since reports completed after this time interval have been shown to be less reliable (Delespaul 1995). In addition, patients with less than 20 reports (out of 60 requested reports) were excluded.

Coping with stress measured in ESM reflected adaptational strategies to cope with daily hassles and was assessed with 3 items rated on 7-point Likert scales (1 *not at all* to 7 *very*): 1) "*I chose this social situation to reduce my stress*", reflecting social coping, 2) "*I chose this activity to reduce my stress*" reflecting activity coping, and 3) "*I chose these substances to reduce my stress*", reflecting substance coping (substances could be coffee, alcohol, cannabis or other illicit drugs or medication). A general measure of coping was computed by summing the three coping items (hereafter: ESM coping; Cronbach's alpha = 0.81).

Distress in ESM is reflected by the amount of negative affect (NA) reported by patients, assessed with the items 'down', 'guilty', 'insecure', 'lonely' and 'anxious' (Cronbach's alpha = 0.74).

Psychotic psychopathology (hereafter: ESM psychopathology) was assessed with 7 ESM items rated on 7-point Likert scales *(1* not at all *to 7* very*)*: *"My thoughts are difficult to express", "I can't get rid of my thoughts", "My thoughts are influenced by other people", "I feel unreal", "I feel threatened", "I feel exalted", "I'm suspicious", "I hear voices", "I see things"* (Cronbach's alpha = 0.70). The use of these items to reflect psychotic psychopathology has been validated previously (Delespaul 1995; Delespaul et al. 2002; Myin-Germeys et al. 2005; Myin-Germeys et al. 2005).

The Maastricht Assessment of Coping Strategies (MACS)

Immediately after the ESM period, coping with psychotic symptoms was assessed using the semi-structured interview Maastricht Assessment of Coping Strategies 24 item version (MACS-24) (Bak et al. 2001; Bak et al. 2001). The interviewer enquired whether the patient had experienced any of 24 symptoms related to psychosis in the last week. If a symptom had been present, the use of any of 14 different coping strategies was assessed (yes or no). Each of these coping strategies was classified in a non-symptomatic or symptomatic coping category. For each coping category, the proportion of times the coping category was used for the symptoms that were present was calculated, resulting in two variables: *symptomatic coping* (hereafter: MACS symptomatic coping) and *non-symptomatic coping* (hereafter: MACS non-symptomatic coping).

Analyses

Multilevel random regression analyses were conducted using the XTREG routine in STATA (StataCorp 2001). In order to test the basic premise that the use of symptomatic coping and non-symptomatic coping represented stable individual differences, the association between MACS symptomatic and non-symptomatic coping was calculated.

MACS coping and ESM coping
In order to test the hypothesis that ESM coping was associated with MACS coping, regression analyses were conducted with ESM coping as the dependent variable and MACS symptomatic coping and MACS non-symptomatic coping as independent variables. ESM psychopathology was added as a covariate in the model as a possible confounder of the association.

MACS coping group and psychopathology-induced distress
In order to test the hypothesis that the contrast between symptomatic and non-symptomatic coping can be validated by differences in symptom-generated distress in daily life, each person was assigned to one of four categories of MACS coping (based on median split): 1 = low symptomatic coping & low non-symptomatic coping; 2 = high symptomatic coping & low non-symptomatic coping; 3 = low symptomatic coping & high non-symptomatic coping and 4 = high symptomatic coping & high non-symptomatic coping (hereafter referred to as: MACS coping group). A regression analyses was conducted with MACS coping group, ESM psychopathology and the interaction between these two variables as independent variables and NA as the dependent variable, in order to examine whether the association between ESM psychopathology and NA would be conditional on, and therefore a characteris-

tic of, non-symptomatic coping but not symptomatic coping. The MACS coping group X ESM psychopathology interaction was fitted and assessed by WALD test with category 1 as the reference category, followed by estimation of psychopathology effect sizes stratified by MACS coping group using the STATA LINCOM routine. Differences in effect sizes between the four categories of MACS coping group were assessed by WALD test**.**

RESULTS

The mean number of valid reports was 40 (SD = 10). The Pearson correlation between symptomatic coping and non-symptomatic coping assessed with the MACS was –0.48 (P < 0.001), indicating that some people tend to use symptomatic coping while others tend to use non-symptomatic coping (Fig. 1).

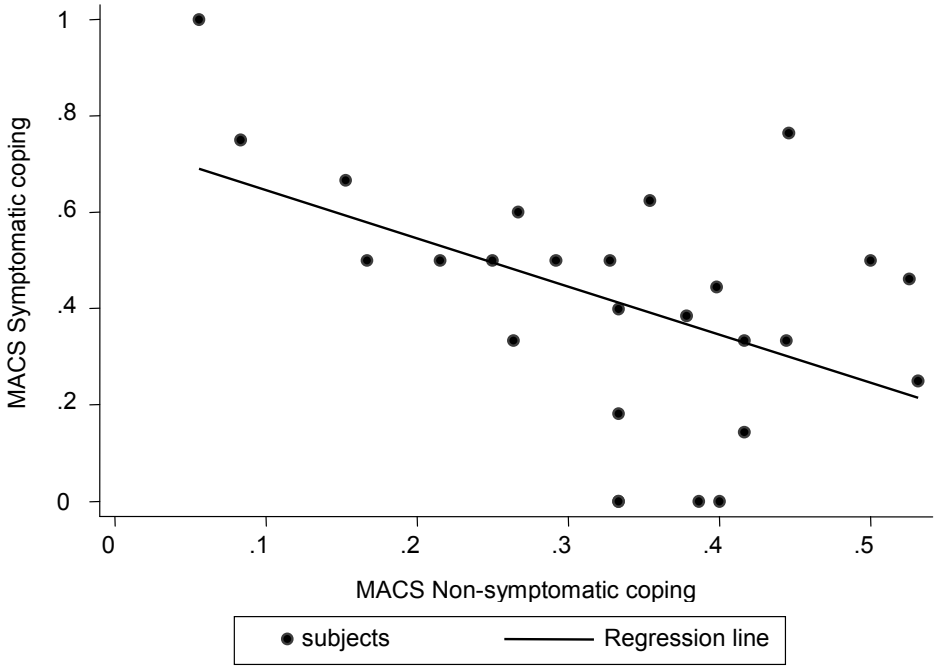

Figure 1. Scatterplot of the association between symptomatic and non-symptomatic coping. A regression line is added. The scatterplot contains only 25 points instead of 26, because 2 subjects had exactly the same values for the variables MACS symptomatic and MACS non-symptomatic coping (MACS symptomatic coping: 0 and MACS non-symptomatic coping:0.33).

MACS coping and ESM coping

The multilevel regression analyses revealed that MACS symptomatic coping was strongly and negatively associated with total amount of ESM coping (B = -7.63 (SE = 3.36); $p < 0.05$), whereas MACS non-symptomatic coping was strongly and positively associated with total amount of ESM coping (B = 18.2 (SE = 6.63); $p < 0.01$). Adjusted for psychopathology, the association remained equally strong and significant (symptomatic coping: B = -7.86 (SE = 3.37); $p < 0.05$; non-symptomatic coping: B = 18.9 (SE = 6.63); $p < 0.01$).

MACS coping group and psychopathology-induced distress

The MACS coping group variable consisted of 5 subjects in category 1; 9 subjects in category 2 and 3; and 3 subjects in category 4. There was a positive and significant interaction between ESM psychopathology and MACS coping group in the model of NA ($\chi^2 = 62.8$, df = 3, $p<0.0001$). There was a significant association between NA and psychopathology in all four coping categories, however, the effect was larger in the higher categories (see table 1).

Table 1. Effect sizes of psychopathology on Negative Affect (NA) for different categories of MACS coping group and WALD tests to examine the difference in the association between psychopathology and NA between the different coping categories

MACS coping categories[a]	NA		
	B	S.E.	p
1 Low Symptomatic / Low Non-symptomatic	0.27	0.12	0.029
2 High Symptomatic/ Low Non-symptomatic	0.40	0.07	< 0.001
3 Low Symptomatic/ High Non-symptomatic	0.80	0.06	< 0.001
4 High Symptomatic/ High Non-symptomatic	1.10	0.07	< 0.001

[a] The effect sizes were all significantly different from each other, except for the difference between category 1 and 2 (1, 2<3<4)

DISCUSSION

The study confirmed the premise that patients who use more symptomatic coping use less non-symptomatic coping and vice versa, suggesting that the tendency to use a certain type of coping to diminish distress caused by psychotic symptoms may represent a stable person characteristic reflecting individual differences. Furthermore, the results of this study demonstrate that symptomatic coping is different in nature compared with non-symptomatic coping. First, patients who use more symptomatic coping to cope with psychotic symptoms, have lower levels of coping in the

flow of daily life. The striking correspondence between retrospective and prospective findings indicates that retrospective reports of coping strategies with psychotic symptoms correspond to the way individuals respond to non-specific stress from moment to moment in the flow of daily life. Given the fact that symptomatic coping may be ineffective as a coping strategy for psychotic symptoms and may reflect a general alteration in coping with daily life stress, it could be productive to help patients who tend to use symptomatic coping strategies to develop more effective coping for example using coping-training (Andres et al. 2000; Wiersma et al. 2001; Wiersma et al. 2004). Second, qualitative differences between symptomatic and non-symptomatic coping were found in the moderation of distress with symptoms. Patients with high levels of non-symptomatic coping have more conscious appraisals of distress associated with their psychotic symptoms, suggesting that the use of non-symptomatic coping is driven by emotional distress and may, therefore, represent functional coping. This is in line with the finding that patients who are the least handicapped by their symptoms use fewer coping strategies (Falloon and Talbot 1981). If non-symptomatic coping is low, however, there is no difference in the association between psychopathology and distress for low and high symptomatic coping. This suggests that patients who tend to use symptomatic coping, always use this form of coping when they suffer from psychotic symptoms, independent from the amount of distress these symptoms generate. Symptomatic coping may represent a more autonomous response independent from distress associated with psychotic phenomena. An interesting exception was formed by the 3 patients who had high levels of both symptomatic coping *and* non-symptomatic coping. These patients also experienced more distress in the context of their psychotic symptoms, in spite of using symptomatic coping. A possible explanation for this finding is that some patients are aware of distress caused by symptoms and sometimes choose to use symptomatic coping as an additional "functional" coping strategy.

Methodological issues

These results should be interpreted in the light of several potential limitations. First, the subject numbers are small. The study should, therefore, be considered a pilot study of coping strategies in psychosis. Second, 9 patients did not comply with the research protocol. It could be argued that attrition may have been differential with regard to exposures and outcomes. However, when the analyses were conducted with the data included of the 4 patients who did complete the ESM but did not have enough valid beeps, the results remained the same.
Third, the ESM measurements of daily life coping are based on subjective reports. Although subjective reports are considered less reliable (e.g. do all subjects inter-

pret or answer the questions identically?), they can be valid whereas the validity of objective approaches should not be taken for granted (Strauss 1994).

Declaration of interest

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Chapter 5

Discussion

The association between childhood trauma and psychosis

Several studies have suggested an association between childhood trauma and the development of clinical and subclinical psychotic symptoms later in life (Janssen et al. 2004; Read et al. 2005). However, it has been argued that methodological flaws limited the conclusions that could be drawn from these previous studies (Morgan and Fisher 2007; Bendall et al. 2008). In chapter 2, we have argued that one way to move forward would be to provide evidence for a possible mechanism underlying the association between trauma and psychosis. In this paper, we argued that sensitization would be a good candidate mechanism. Patients with a psychotic disorder tend to react with stronger negative emotions and psychotic symptoms to stressors occurring in daily life than a control group (Myin-Germeys et al. 2005); in other words: they report an increased sensitivity to stress. In chapter 2, we demonstrated that a) patients with psychosis report more trauma compared to their relatives and controls, and b) that stress-sensitivity appears to be stronger in patients who experienced trauma in their childhood compared to those without these traumatic experiences. These findings support the hypothesis that traumatic experiences may sensitize people for the stresses they encounter later in life. An interesting finding was that experiences of stress not only increased negative affect, patients also reported increases in subtle psychotic experiences and this effect was most pronounced in patients with childhood trauma. It is attractive to hypothesize that the cumulative increase in these subtle psychotic experiences may eventually pull patients over the line to develop a full-blown psychotic episode.

These data thus support the notion that increased sensitivity to stress which is found in patients with psychosis, but also in their first-degree relatives, is not only caused by genetic vulnerability, but is also influenced by environmental determinants such as childhood trauma (chapter 2). The environment may thus shape the vulnerability to develop psychosis.

The finding that exposure to trauma is associated with an increased sensitivity to stress in adulthood may have a biological basis since exposure to trauma has been found to alter the HPA axis, which is one of the major systems involved in the stress-response (De Bellis et al. 1994; Heim et al. 2000). Furthermore, increased HPA axis activity has also been associated with psychosis as is discussed in chapter 3 (van Winkel et al. 2008; Walker et al. 2008) and with increased dopamine activity in certain brain regions, in particular the mesolimbic system, which, in turn, appears to be associated with psychosis (Laruelle 2000).

Alterations in the HPA axis activity and the development of psychotic symptoms

In chapter 3, we investigated whether altered HPA axis activity may be a mechanism underlying the development of sub-clinical psychosis. It was shown that first-degree relatives have a higher diurnal cortisol level, but also a stronger cortisol response to a stressor than healthy controls. Furthermore, deviations from the normal cortisol curve are associated with increased levels of psychotic experiences in first-degree relatives (chapter 3).

The finding that first-degree relatives have higher basal cortisol levels is in line with previous findings of elevated basal cortisol levels in patients with a psychotic disorder (van Winkel et al. 2008). It is suggested that these elevated diurnal cortisol levels in psychotic patients and their siblings are associated with a reduced negative feedback system of the HPA–axis (Phillips et al. 2006). Combined with the finding of an increased cortisol response to a stressor, this suggests that the HPA axis of first-degree relatives is hypersensitive compared to subjects of the normal populations.

The second question is how this would be related to the development of psychosis. Several studies suggested that hyperreactivity of the dopamine system may be involved in psychosis. According to the dopamine sensitization theory, an excessive dopamine response would cause positive symptoms of psychosis in patients (Laruelle and Abi-Dargham 1999), possibly because stimulus independent release of dopamine may lead to aberrant assignment of salience to external objects and internal representations (Kapur 2003). It has been suggested that the hyperreactivity of the dopamine system may be associated with a hypersensitive HPA axis (Walker et al. 2008), since rises in cortisol may cause dopaminergic elevations. Evidence suggests that glucocorticoid secretion may increase dopamine activity in certain brain regions, in particular the mesolimbic system (Walker et al. 2008), however, strong evidence is lacking. Our finding that momentary deviations from the normal cortisol curve were significantly associated with increases in psychotic symptomatology (chapter 3) could provide indirect evidence for this putative association, possibly supporting the notion that cortisol may be involved in the pathogenesis of psychotic symptoms.

However, one could also hypothesize that the distress associated with the psychotic experiences increases cortisol levels, as negative affect appears to increase cortisol levels (van Eck et al. 1996; Smyth et al. 1998; Hanson et al. 2000; Jacobs et al. 2007) and psychotic experiences are related to increases in anxiety, negative affect and distress (Myin-Germeys et al. 2001; Freeman and Garety 2003). This would also fit with the findings of (Thompson et al. 2007) who found increased cortisol reactions to daily hassles to be associated with anxiety and depression, but not psychosis in subjects at ultra-high risk for psychosis. However, this study did not measure stress

in daily life and chapter three shows that the relatives still show an increase in psychotic symptoms related to cortisol deviations after controlling for negative affect. This suggests that psychosis induced negative affect increasing cortisol levels is unlikely to be the sole explanation for the association between cortisol deviations and increased psychotic experiences.

The difference in findings in the current study compared to previous laboratory studies investigating the cortisol response to a stressor is probably due to a difference in methodology. First of all, the stressors used in laboratory paradigms are of a different nature than the small daily hassles that people encounter in their everyday life. For example, most laboratory designs use a metabolic stressor. However, it appears that especially small psychological stressors have an influence on psychotic symptoms (Norman and Malla 1991; Myin-Germeys et al. 2005). There are only a few studies investigating a psychological stressor with a public speaking task. However, this task is still very different in nature compared to the small daily stressors people encounter in their daily life. Second, almost all previous studies have investigated the cortisol response to a laboratory stressor in patients taking antipsychotic medication, which can influence cortisol levels (Meltzer 1989; Wik 1995). It has been suggested that antipsychotic medication possibly leads to a decrease in cortisol level through associated anticholinergic activity.

Therefore, in chapter 3 relatives of patients with psychosis were investigated, because they do not use antipsychotic medication and do not experience the distress associated with psychotic experiences, but they do show increases in subtle psychotic symptoms after stressful experiences. Also, these relatives were investigated in their daily life to ensure the investigation of real stressors in everyday life. The results show that people who are vulnerable to develop a psychosis show an increased cortisol response to stressful experiences (chapter 3), which is in line with previous findings of a daily-life study (Thompson et al. 2007)

How do people cope with the stress caused by psychotic symptoms?

Psychotic symptoms may not only be caused by environmental stressors, the symptoms in itself may also cause stress, thus generating a need for patients to cope with their symptoms. In chapter four we investigated a coping strategy that is often used by patients with psychosis, but that appears to be an ineffective method (symptomatic coping or going along with the symptoms) and we compared this method with other forms of coping (non-symptomatic coping). The findings of chapter 4 show that the tendency to use a certain type of coping may represent a stable person characteristic. Furthermore, it was shown that people using mainly symptomatic coping as a strategy use fewer coping to deal with the stress occurring in the flow of

daily life. This suggests that they are ineffective copers in general. Furthermore, patients using non-symptomatic coping with symptoms, have more conscious appraisals of the distress that is associated with their psychotic symptoms, suggesting that the use of non-symptomatic coping is driven by emotional distress and may, therefore, represent functional coping (chapter 4). However, sometimes people tend to use both symptomatic and non-symptomatic coping strategies and they also appear to have conscious appraisals of the distress caused by the symptoms (chapter 4). Probably, they are able to sometimes choose to use symptomatic coping as an additional 'functional' coping strategy. Patients who tend to use mainly symptomatic coping, always use this form of coping when they suffer from psychotic symptoms, independent from the amount of distress these symptoms generate. Symptomatic coping may represent a more autonomous response independent from distress associated with psychotic phenomena (chapter 4).

A possible explanation for the difference between symptomatic and non-symptomatic coping can be a difference in what is referred to as "insight" between patients who tend to use symptomatic coping and patients who tend to use non-symptomatic coping. The choice of coping strategies may be related to the amount of insight in the disorder. Patients with psychotic symptoms often have altered insight: they are unaware of their symptoms, the consequences of the disorder and the need for treatment (Amador et al. 1991; Amador et al. 1994; David et al. 1995). Patients with a lack of insight do not label their experiences as a sign of illness and therefore may be more likely to resort to symptomatic coping. This raises the question whether symptomatic coping is an actual coping strategy, as it may be considered an autonomous response to symptoms.

The affective pathway to psychosis

The findings in chapter 2 and 3 underscore the importance of stress-reactivity as a central mechanism in the development of psychosis. These findings fit within a recent framework suggesting that altered stress-sensitivity may be an independent and specific mechanism underlying the positive symptoms of psychosis.

In view of recent developments of DSM, it has been suggested that symptom dimensions rather than diagnostic categories may constitute more homogeneous entities with similar symptom patterns, aetiology, prognosis and possibly treatment (McGorry et al. 1998; Cuesta et al. 2006; Allardyce et al. 2007). Factor analyses have distinguished two to five symptom dimensions (Peralta et al. 1994; Kitamura et al. 1995; McGorry et al. 1998; Peralta and Cuesta 1999; Lindenmayer et al. 2004; Serretti and Olgiati 2004; Murray et al. 2005; Dikeos et al. 2006), the two most prominent being a positive and a negative dimension. Whereas the negative symptom

dimension has been linked to cognitive impairments via the so-called cognitive pathway (Van Os and Verdoux 2001; Dominguez et al. 2008), the positive dimension appears to be specifically characterized by altered stress-sensitivity (Myin-Germeys et al. 2003; Lataster et al. submitted) which is independent from cognitive performance (refs). The latter has been called the affective pathway (Myin-Germeys and van Os 2007). Previous studies already suggested that especially the positive symptoms are more sensitive to aversive environmental influences (Murray et al. 1992). The current thesis further strengthened the notion of an affective pathway to psychosis, by demonstrating a) that previous experiences of trauma could increase current stress-reactivity, possibly explaining the putative association between trauma and psychosis; and b) that increased cortisol-reactivity may be the underlying biological mechanism. The latter fits with the earlier notion suggested by Murray and colleagues that alterations at the level of neurotransmitter signalling, for example mesolimbic hyperdopaminergia possibly secondary to abnormal activation of the HPA axis, may play an important role in the development of the positive psychosis syndrome (Murray et al. 1992).

Vulnerability-stress model

The findings presented in this thesis can be easily understood within a vulnerability-stress framework that is often used to explain the emergence of psychotic symptoms (Zubin and Spring 1977; Zubin et al. 1983). The vulnerability-stress model states that people develop symptoms due to an interplay between environmental factors and an underlying vulnerability. People will only develop psychotic symptoms if the stressors they encounter in their life exceed a threshold, which is dependent on the level of vulnerability. In this thesis, it was shown that first-degree relatives of patients with a psychotic disorder, who are genetically at risk to develop a psychosis, differ in their HPA axis activity compared to a group of healthy controls (chapter 3). These deviations in HPA axis activity may represent part of the underlying vulnerability for psychosis, since 1) first-degree relatives reported the alterations in HPA axis activity, and 2) more importantly, deviations from the normal cortisol curve were associated with psychotic experiences. Chapter 2 underscored the importance of environmental factors that may be associated with the development of psychosis. At the same time, this study showed that early trauma may also increase the vulnerability to develop psychosis later in life, since early trauma sensitized people for later exposures to stress. It underscores the complex nature of the interaction between genes and environment. An interesting finding was that experiences of childhood trauma were rare in the relatives group. Following the vulnerability-stress model, one could argue that relatives had low levels of trauma

because they would have developed psychosis if they had been exposed to trauma, given their underlying vulnerability for psychosis.
Chapter three has shown that HPA axis aberrations appear to be an underlying vulnerability for psychosis. However, previous research has also shown that stressful experiences such as childhood trauma, may alter HPA axis functioning (De Bellis et al. 1994; Heim et al. 2000), which has been suggested to be the underlying mechanism of the process of sensitization caused by childhood trauma that was found in chapter two. Therefore, the experience of childhood trauma in patients with a psychotic disorder may further impair an already deviated HPA axis.
Finally, most patients with psychosis appear to have an increased sensitivity to stress which, in turn, makes them vulnerable to develop a psychosis (see figure 1). However, psychotic symptoms can also cause stress, which makes it necessary for people to find ways to cope with their symptoms. Apparently, patients often use the ineffective symptomatic coping method (Bak et al. 2001)(chapter 4), which then fails to reduce the distress associated with the psychotic symptoms. The failure to reduce stress caused by the symptoms makes them again more vulnerable to develop new symptoms. This demonstrates the importance of effective coping methods.

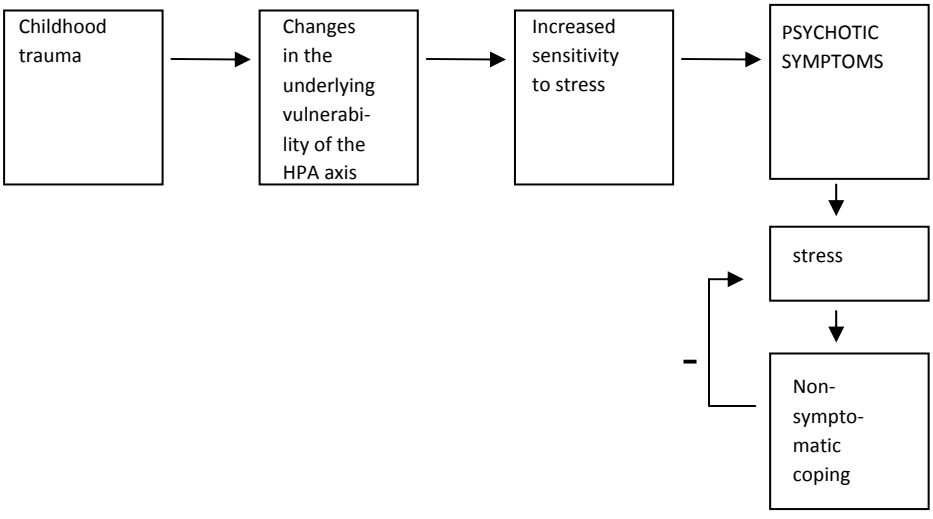

Figure 1. Schematic representations of the interaction between stressful experiences and psychotic symptoms.

Implications for clinical practice

Clearly, the findings of this thesis are still a long way from offering direct therapeutic insight.

However, several recommendations for treatment can be made. First of all, the finding that childhood trauma may be associated with psychosis through a mechanism of sensitization, suggests that it may be important to tailor treatment aimed at reducing sensitivity to stress in daily life. One way to do so is by reducing stress in the social environment of the patient, for example by teaching people how to use self-relaxation or distraction techniques, although this does not work in early psychosis (Hodel et al. 1998). Another possibility is to use Cognitive Behavioural Therapy (CBT) to remediate stress-sensitivity. Previous studies have shown that Cognitive Behavioural Therapy (CBT) reduces psychotic symptoms (Pilling et al. 2002) and distress caused by psychotic symptoms (Valmaggia et al. 2005), it has beneficial effects on depression, as well as on delusional distress and social functioning (Garety et al. 2008). The results of this thesis suggest that it may be useful to extend the therapy in such a way that it also focuses on emotional sensitivity to stress in daily life.

In addition, it may be important to prevent the process of sensitization in the earliest initial phase. The prospective study by Spataro et al. (Spataro et al. 2004) found no association between childhood trauma and the later development of psychosis. One possible explanation of this failure to find an association is that the included cases were derived from police or other official reports. These children were thus recognised as being a victim of trauma and possibly received treatment, which may have prevented or reversed the sensitization process.

Furthermore, the finding in the third chapter that atypical HPA-patterns appear to be inherent characteristics of individuals vulnerable to psychosis may suggest a new target for pharmacological interventions, although more evidence is needed supporting a causal role of HPA-axis dysfunction in psychosis.

Finally, effective coping strategies may be useful to reduce the distress associated with the psychotic symptoms, thus improving quality of life. In chapter 4 it is shown that the tendency to use a specific type of coping is a stable trait, suggesting that it would be difficult to change the coping pattern. Still, it may be useful to help patients who tend to use the ineffective strategy of symptomatic coping (going along with symptoms) to develop more effective coping strategies, for example by using coping training.

Directions for further research

To conclude, this thesis does not pretend to fully capture the complexity of the interaction between stress and psychosis. First of all, the results of this thesis show that trauma appears to be a risk factor to develop a psychosis and that sensitization may be the underlying mechanism. However, trauma is only one of the many stressful experiences that can cause a psychotic disorder. Previously, several other stressful experiences have been discovered as risk factors for psychosis, such as urban environments (Marcelis et al. 1999; Janssen et al. 2003; Kirkbride et al. 2006) and discrimination (Janssen et al. 2003).Therefore, it is important to investigate whether the process of sensitization is specific for trauma or whether it is also the mechanism that causes psychosis after other stressful experiences.
Secondly, this thesis shows that the HPA axis appears to be involved in psychosis. However, in this study, only relatives of patients with a psychotic disorder were investigated. This was a deliberate decision, because almost all patients use antipsychotic medication, which in itself influences the HPA axis. However, it would be important to extend these findings to a – preferentially unmedicated- patient population. Furthermore, because the dopamine sensitization theory states that an excessive dopamine response can cause positive symptoms of psychosis in patients (Laruelle and Abi-Dargham 1999) and because there appears to be a link between the HPA axis and the dopamine system, it is important to find ways to investigate dopamine directly. It is still impossible to investigate dopamine in daily life using the Experience Sampling Method. However, it would be a possibility to investigate dopamine after a stress task in the laboratory, using D2 binding in a PET paradigm.
Finally, chapter 4 of this thesis shows that symptomatic coping is an ineffective coping method and it is suggested that patients use this strategy more because of a lack of insight in the disorder. Therefore, it would be interesting to investigate whether insight indeed is a mechanism mediating the coping strategies used. In addition, it would be important to evaluate whether psychological therapies can change coping strategies and whether this would be helpful in improving quality of life.

Conclusions

The findings of this thesis are still a long way from unravelling all of the aspects of the interaction between stress and psychosis. However, a few important contributions have been made. First of all, the results of this thesis further strengthen the notion of an association between childhood trauma and psychosis by showing a) that levels of childhood trauma are higher in a patient group than in healthy con-

trols and b) that the underlying mechanism of this association appears to be the process of sensitization. Secondly, this thesis has found an overactivated HPA axis in individuals at genetic risk for psychosis compared to controls. Furthermore, an association was found between deviations in cortisol and momentary psychosis level, which suggests that changes in cortisol may be involved in the pathogenesis of psychotic symptoms. Finally, this thesis has investigated coping with psychotic symptoms and has found that effective coping may be associated with the tendency to develop conscious appraisals of distress.

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Summary

Samenvatting

Summary

This thesis investigated stress as a central mechanism in psychosis. It was argued that sensitivity to stress is important both in the aetiology and development of psychosis, but also in the subsequent consequences of psychosis. In this dissertation, three elements related to stress were investigated. First, it was investigated whether traumatic experiences may induce increased sensitivity to the smaller stresses in life, a mechanism that we call sensitization. Second, the biological underpinnings of increased stress-sensitivity as a vulnerability marker for psychosis were investigated. Third, it was argued that psychotic symptoms may also cause distress and this study investigated whether patients with psychosis were able to deal with the distress associated with symptoms.

Chapter 1 provides an introduction to the concept of psychosis and psychotic symptoms, which may exist as a continuum in nature, as opposed to the dichotomy between disorder and no disorder that is used in clinical practice. For a long time, stress has been implicated in the aetiology of this psychosis continuity. According to the vulnerability-stress model, psychiatric symptoms will emerge whenever a threshold of stressors exceeds the individual's vulnerability level, the latter being a stable characteristic. However, it has been argued that several questions with regard to this vulnerability-stress interplay remain unanswered. First, it remains unclear how environmental stressors, identified in epidemiological research, impact on momentary stress-sensitivity, an endophenotype associated with psychosis. It has been argued that sensitization might be a central underlying pathway leading from environmental stress to psychosis. However, evidence to date is lacking. Second, the biological mechanisms underlying this increased stress-response remain unclear. Almost no research to date has focused on possible biological pathways, underlying the association between stress and psychosis. Third, a very important, but often discarded cause of stress are the psychotic symptoms themselves. Hearing voices commenting in your head or being afraid that someone would poison you, could cause enormous amounts of distress. It is therefore important to investigate how patients deal with these forms of stress as well.
Finally, the power of studying first-degree relatives of patients with psychosis is discussed, as they do have an underlying vulnerability to develop psychosis, but do not experience the stress associated with experiencing psychotic symptoms. Also the Experience Sampling Method (ESM) is discussed as a reliable and valid method to study psychotic symptoms as well as cortisol measures in the realm of daily life.

Chapter 2 describes a study examining a possible mechanism underlying the association between childhood trauma and psychosis. It has been argued that the notion

that traumatic experiences in childhood (CT) may predict later psychotic outcomes would be strengthened if a plausible mechanism could be demonstrated. Given the fact that previous work has suggested that increased daily life stress-sensitivity is part of the behavioural expression of psychosis liability, the possible mediating role of childhood trauma was investigated. This study included 50 patients diagnosed with a psychotic episode, 55 siblings of patients with a psychotic disorder and 45 healthy controls. The Experience Sampling Method was used to assess stress-reactivity in daily life and childhood trauma was assessed using the Childhood Trauma Questionnaire. First, the results confirmed previous findings of an association between childhood trauma and psychotic symptoms later in life, with higher levels of childhood trauma in the patient group compared to the relatives and controls. Also, a significant interaction was found between stress and childhood trauma in the patient group on both negative affect and psychotic intensity, indicating an effect of childhood trauma on stress-sensitivity. Thus, higher rates of trauma in patients versus control as well as evidence for an underlying sensitization process provided further support for the putative association between childhood trauma and psychosis.

Chapter 3 focuses on the biological underpinnings underlying increased stress-sensitivity in psychosis. First-degree relatives of patients with a psychotic disorder react with subtle increases in non-clinical psychotic experiences when faced with stress. The study presented in chapter 3 investigated to what degree these behavioural changes are predicted by changes in the hypothalamic-pituitary-adrenocortical axis, as indexed by cortisol level. The sample consisted of 58 siblings of patients with a psychotic disorder and 62 healthy control subjects. The Experience Sampling Method was used to assess stress and psychotic experiences in daily life and to sample salivary cortisol levels. Multilevel analyses revealed higher diurnal cortisol level and heightened cortisol to stress in siblings compared to controls. Diurnal cortisol slope did not differ between the two groups, but transient deviations from an individual's modelled cortisol curve significantly predicted increases in intensity of subclinical psychotic experiences, particularly in the sibling group. The findings were compatible with HPA axis overactivity in individuals at genetic risk for psychosis. The data also suggested an association between increased cortisol reactivity and the intensity of psychotic-like experiences, although the direction of this association remains to be elucidated.

In **Chapter 4** a study is presented investigating the coping mechanisms used by patients to cope with the stress of their symptoms, making a distinction between symptomatic coping (going along with symptoms) and non-symptomatic coping strategies. Previous research has suggested that going along with psychotic symp-

toms (symptomatic coping) is less effective than other coping strategies with psychotic symptoms. This study aimed to validate such findings using a momentary assessment strategy of coping with stress in daily life. Results of 35 patients studied with ESM and the Maastricht Assessment of Coping Strategies (MACS) showed that Symptomatic and Non-symptomatic Coping were negatively associated with each other. Symptomatic Coping was negatively associated with the level of coping in daily life and Non-symptomatic Coping was positively associated. Non-symptomatic Coping, but not Symptomatic Coping, predicted appraisals of distress associated with psychotic symptoms. It was concluded that effective coping may be associated with the tendency to develop conscious appraisals of distress associated with psychotic symptoms.

Chapter 5 provides a summary of the findings and evaluates them in the light of previous research findings on stress and psychosis. In this chapter, it is argued that the findings underscore the importance of stress-reactivity as a central mechanism in the development of psychosis. The findings fit within a recent framework suggesting that altered stress-sensitivity may be an independent and specific mechanism underlying the positive symptoms of psychosis.
It was also discussed that the findings of this thesis fit within the vulnerability-stress model, which states that people develop symptoms due to an interplay between environmental factors and an underlying vulnerability. Deviations in HPA axis activity may be part of the underlying vulnerability for psychosis since persons at risk for psychosis seem to have an hyperactive HPA axis and deviations in cortisol are associated with sub-clinical psychotic symptoms. Chapter 2 underscored the importance of environmental factors that may be associated with the development of psychosis. At the same time, this study showed that early trauma may also increase the vulnerability to develop psychosis later in life, since early trauma sensitized people for later exposures to stress. Finally, since symptoms may also cause distress, it is necessary for patients to find efficient ways to cope with their symptoms. A model is proposed integrating the findings of the current thesis. The chapter ends with some clinical implications of the findings of this thesis and suggestions for further research.

Samenvatting

In dit proefschrift werd onderzoek gedaan naar stress als centraal mechanisme bij psychose. Er werd beargumenteerd dat gevoeligheid voor stress belangrijk is bij zowel de etiologie en het ontstaan van een psychose als ook bij de daaropvolgende consequenties van een psychose. In dit proefschrift werden drie elementen onderzocht die gerelateerd zijn aan stress. Ten eerste is onderzocht of traumatische ervaringen een toegenomen gevoeligheid voor de kleinere stressoren in het dagelijks leven kunnen induceren, een mechanisme dat we sensitizatie noemen. Ten tweede zijn de biologische mechanismen die mogelijk ten grondslag liggen aan verhoogde stressgevoeligheid als een kwetsbaarheid marker voor psychose onderzocht. Als derde werd beargumenteerd dat psychotische symptomen ook stress kunnen veroorzaken en in een laatste studie werd onderzocht of patiënten met psychose in staat waren om te gaan met de stress die geassocieerd is met hun symptomen.

Hoofdstuk 1 geeft een introductie over de concepten psychose en psychotische symptomen die in de natuur als een continuüm lijken te bestaan, in tegenstelling tot de dichotomie tussen stoornis en geen stoornis die in de klinische praktijk gebruikt wordt. Al lange tijd wordt gedacht dat stress een rol speelt in de etiologie van deze psychotische continuïteit. Volgens het kwetsbaarheid-stress model ontstaan psychiatrische symptomen als een hoeveelheid stressoren het niveau van kwetsbaarheid van een persoon, een stabiele eigenschap, overschrijdt. Echter, bepaalde vragen omtrent deze interactie tussen kwetsbaarheid en stress zijn tot nu toe nog onbeantwoord. Ten eerste blijft het onduidelijk hoe stressoren uit de omgeving, die in epidemiologisch onderzoek zijn aangetoond, inspelen op stress-gevoeligheid van moment tot moment, een endophenotype dat geassocieerd is met psychose. Er wordt beargumenteerd dat sensitizatie een centraal onderliggend mechanisme zou kunnen zijn dat ervoor zorgt dat omgevingsstress leidt tot psychose. Echter, bewijs ontbreekt tot nu toe nog. Ten tweede, de biologische mechanismen onderliggend aan deze verhoogde stressreactie zijn nog onduidelijk. Tot nu toe is er bijna geen onderzoek gedaan naar mogelijke biologische paden, die ten grondslag kunnen liggen aan de associatie tussen stress en psychose. Ten derde, een zeer belangrijke, maar vaak genegeerde, oorzaak van stress zijn de psychotische symptomen zelf. Het horen van stemmen die commentaar geven in je hoofd of bang zijn dat iemand je wil vergiftigen kan enorme stress met zich meebrengen. Daarom is het belangrijk om ook te onderzoeken hoe patiënten met deze vorm van stress omgaan.
Als laatste wordt het belang van het onderzoeken van eerstegraads familieleden van patiënten met psychose bediscussieerd, omdat zij een onderliggende kwetsbaarheid hebben om een psychose te ontwikkelen, maar niet de stress ervaren die geassocieerd is met de psychotische symptomen. Ook wordt de Experience Sam-

pling Methode (ESM) besproken als een betrouwbare en valide methode om psychotische symptomen te bestuderen, alsook om cortisol te meten, in de context van het dagelijks leven.

Hoofdstuk 2 beschrijft een studie die onderzoek doet naar een mechanisme dat mogelijk ten grondslag ligt aan de associatie tussen trauma in de kindertijd en psychose. In dit hoofdstuk werd beargumenteerd dat de idee dat traumatische ervaringen in de kindertijd het ontstaan van latere psychotische ervaringen kan voorspellen, versterkt kan worden als een geloofwaardig onderliggend mechanisme gevonden wordt. Doordat resultaten van eerdere studies hebben gesuggereerd dat verhoogde stressgevoeligheid in het dagelijks leven een onderdeel is van de gedragsmatige uiting van de kwetsbaarheid voor psychose, werd in dit hoofdstuk de mediërende rol van trauma in de kindertijd onderzocht. Deze studie includeerde 50 patienten die gediagnosticeerd werden met een psychose, 55 broers/ zussen van patienten met een psychotische stoornis en 45 gezonde controle personen. Om stressgevoeligheid in het dagelijks leven te meten werd gebruik gemaakt van de Experience Sampling Methode en traumatische ervaringen in de kindertijd werden in kaart gebracht met de Childhood Trauma Questionnaire (Jeugd Trauma Vragenlijst). Ten eerste repliceerden de resultaten eerdere bevindingen van een associatie tussen trauma in de kindertijd en psychotische symptomen later in het leven, met meer traumatische ervaringen in de patiënt groep ten opzichte van de broers/zussen en de controles. Ook werd er een significante interactie gevonden tussen stress en trauma in de kindertijd in de patiëntengroep op zowel negatieve emoties als psychose intensiteit. Dit geeft aan dat er een effect is van trauma in de kindertijd op stressgevoeligheid. Dus, meer trauma in de kindertijd bij patiënten ten opzichte van controles, alsook bewijs voor een onderliggend sensitizatie proces dient als extra bewijs voor de waarschijnlijke associatie tussen traumatische ervaringen in de kindertijd en psychose.

Hoofdstuk 3 richt zich op de biologische mechanismen die ten grondslag liggen aan verhoogde stress-gevoeligheid bij psychose. Eerstegraads familieleden van patiënten met een psychotische stoornis reageren met subtiele toenamen in subklinische psychotische ervaringen als ze geconfronteerd worden met stress. De studie die gepresenteerd werd in hoofdstuk 3 heeft onderzocht in welke mate deze gedragsmatige veranderingen voorspeld kunnen worden door veranderingen in de hypothalamus-hypofyse-bijnier as, oftewel de HPA as, weergegeven door het cortisol niveau. De onderzoeksgroep bestond uit 58 broers/ zussen van patiënten met een psychotische stoornis en 62 gezonde controle proefpersonen. De Experience Sampling Methode werd gebruikt om stress en psychotische ervaringen in kaart te brengen en om cortisol te verzamelen. Multilevel analyses lieten hogere dagelijkse cor-

tisol niveaus en een hogere cortisolreactie op stress zien in de broers en zussen ten opzichte van de controle groep. De helling van de cortisol curve verschilde niet tussen de twee groepen, maar afwijkingen van de gemodelleerde curve per individu voorspelden significante toenamen in de intensiteit van subklinische psychotische ervaringen, met name in de groep broers en zussen. Deze bevindingen komen overeen met overactiviteit van de HPA as in proefpersonen met een verhoogd genetisch risico op psychose. De data suggereren ook dat er een associatie bestaat tussen verhoogde cortisol reactiviteit en de intensiteit van psychose-achtige ervaringen, hoewel de richting van deze associatie nog opgehelderd moet worden.

In **hoofdstuk 4** wordt een studie beschreven die de coping mechanismen heeft onderzocht die patiënten gebruiken om te kunnen omgaan met de stress die veroorzaakt wordt door hun symptomen. Er werd een onderscheid gemaakt tussen symptomatische coping- (meegaan met je symptomen) en niet-symptomatische copingstrategieën. Eerder onderzoek heeft gesuggereerd dat het meegaan met je psychotische symptomen (symptomatische coping) minder effectief is dan andere copingstrategieën voor psychotische symptomen. Het doel van deze studie was om zulke bevindingen te valideren door gebruik te maken van een zogenaamde momentary assessment strategie van coping met de stress van het dagelijkse leven. Resultaten van 35 patiënten, bestudeerd met de ESM en de Maastricht Assessment of Coping Strategies (MACS), lieten zien dat symptomatische en niet-symptomatische coping negatief met elkaar geassocieerd waren. Symptomatische coping was negatief geassocieerd met het niveau van coping in het dagelijks leven en niet-symptomatische coping was positief geassocieerd hiermee. Niet-symptomatische coping kon waarderingen van stress geassocieerd met psychotische symptomen voorspellen, in tegenstelling tot symptomatische coping. Er werd geconcludeerd dat effectieve coping geassocieerd kan zijn met de neiging om bewuste inschattingen te maken van de stress die geassocieerd is met psychotische symptomen.

Hoofdstuk 5 geeft een samenvatting van de bevindingen en evalueert deze in het licht van eerdere onderzoeksbevindingen over stress en psychose. In dit hoofdstuk wordt beargumenteerd dat de bevindingen het belang benadrukken van stress-reactiviteit als een centraal mechanisme in de ontwikkeling van psychose. De bevindingen passen binnen een recente theorie die suggereert dat veranderde stress-gevoeligheid een onafhankelijk en specifiek mechanisme is dat ten grondslag ligt aan de positieve symptomen van psychose.
Er wordt bovendien bediscussieerd dat de bevindingen van dit proefschrift passen binnen het kwetsbaarheid-stress model, dat zegt dat mensen symptomen ontwikkelen door een samenspel tussen omgevingsfactoren en een onderliggende kwets-

baarheid. Afwijkingen in de activiteit van de HPA as zou onderdeel kunnen zijn van de onderliggende kwetsbaarheid voor psychose, aangezien personen met een verhoogd risico voor psychose een hyperactieve HPA as lijken te hebben en afwijkingen in cortisol zijn geassocieerd met sub-klinische psychotische symptomen. Hoofdstuk twee benadrukt het belang van omgevingsfactoren die geassocieerd zijn met de ontwikkeling van een psychose. Ook liet deze studie zien dat vroege traumatische ervaringen ook de kwetsbaarheid om een psychose te krijgen verhoogt, aangezien trauma's in de kindertijd mensen sensitizeren voor latere blootstellingen aan stress. Als laatste, omdat symptomen ook stress kunnen veroorzaken, is het noodzakelijk voor patiënten om efficiënte manieren te zoeken om met hun symptomen om te gaan. Uiteindelijk wordt een model gegeven waarin de bevindingen van dit proefschrift worden geïntegreerd. Het hoofdstuk eindigt met een aantal klinische implicaties en suggesties voor verder onderzoek.

Dankwoord

Curriculum vitae

List of Publications

Dankwoord

Zoals velen weten, is het schrijven van dit proefschrift over stress zelf ook met de nodige stress gepaard gegaan. Gelukkig heb ik vanuit mijn omgeving op verschillende manieren veel steun ontvangen tijdens de totstandkoming van dit boekje. Ik vind het dan ook erg belangrijk om hier even bij stil te staan en iedereen te bedanken.

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Curriculum Vitae

Mariëlle Lardinois werd geboren op 15 april 1980 te Heerlen. Nadat zij in 1998 haar VWO diploma (gymnasium) behaalde, studeerde zij een jaar biologie aan de Universiteit Utrecht. In 1999 startte zij met de opleiding psychologie aan de Universiteit Maastricht. In juni 2004 studeerde zij af in de richting biologische psychologie met als afstudeervarianten neuropsychologie en psychopathologie. Haar klinische en wetenschapsstage vervulde ze bij de Mondriaan Zorggroep te Heerlen en de Capaciteitsgroep Psychiatrie en Neuropsychologie van de Faculteit Geneeskunde. In september 2004 werd ze bij deze capaciteitsgroep aangesteld als promovendus. Naast haar promotieonderzoek verzorgde ze onderwijs voor de Faculteit Geneeskunde. Per 1 september 2009 is ze werkzaam als docent bij de Faculty of Health Medicine and Life Sciences van de Universiteit Maastricht.
Mariëlle Lardinois woont samen met Koen Hermkens. Samen hebben zij een dochter, Eline en in maart 2010 verwachten zij hun tweede kindje.

LIST OF PUBLICATIONS

Articles

Lardinois, M., Myin-Germeys, I., Bak, M., Mengelers, R., Van Os, J., Delespaul, Ph. The dynamics of symptomatic and non-symptomatic coping with psychotic symptoms in the flow of daily life. Acta Psychiatrica Scandinavica, 2007. 116: p. 71-75.

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Lardinois M., Nicolson, N.A., Lataster, T., Sulon, J., Mengelers, R., Van Os, J., Myin-Germeys, I. Stress and cortisol in subjects at risk for psychosis: an experience sampling study. Submitted

Lataster, T., Collip, D. , **Lardinois, M.**, Van Os, J., Myin-Germeys, I. Evidence for a familial correlation between increased reactivity to stress and positive psychotic symptoms. Submitted

Lataster, T., Valmaggia, L., **Lardinois, M.**, Van Os, J., Myin-Germeys, I. Stress-reactivity in psychosis: a specific mechanism underlying the positive symptoms. Submitted

Lataster, T., Valmaggia, L., **Lardinois, M.**, Van Os, J., Myin-Germeys, I. Stress-reactivity and cognition independent risk factors for psychosis: a replication study. Submitted

Lataster, J., van Os, J., de Haan, L., Thewissen V., Bak, M., Lataster, T., **Lardinois, M.**, Delespaul, P., Myin-Germeys, I. Emotional Experience and Estimates of D2 Receptor Occupancy in Psychotic Patients Treated with Haloperidol, Risperidone, or Olanzapine: an Experience Sampling Study. Submitted

Abstracts

Lardinois, M., Myin-Germeys, I., Bak, M., van Os, J. & Delespaul, Ph. (2006). Symptomatic and non-symptomatic coping: dynamics in daily life. *Schizophrenia Research, 81 Supplement,* 124-125

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